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RECENT ADVANCES IN THE STUDY OF TYPHUS FEVER*

BY HANS ZINSSER, M.D.†

Abstract

THE paper consisted of a brief description of the studies on typhus fever which have been carried on during the last six years at the Harvard Medical School and elsewhere. Preliminary corroborative investigations showed that the virus of typhus was not filtrable and that Mooser's observation of rickettsia bodies in the tunica vaginalis of infected guinea pigs was accurate. Further work led to the definite establishment of the etiologic role of *Rickettsia prowazeki* which, although accepted by many, had not been conclusively demonstrated.

The next objective was the attempt to obtain experimental support for the suggestion afforded by the epidemiologic studies of Maxcy on typhus fever in the southeastern United States that a rodent reservoir of the virus, with an insect vector not necessarily the louse, might well exist. Studies carried out in Mexico City at the time of a typhus epidemic revealed the virus in a number of brains removed from rats caught in the Belem Prison where the epidemic had started. At approximately the same time, Dyer demonstrated the infectious nature of rat fleas taken from rats trapped in typhus foci in Maryland. It thus appears that there are two varieties of typhus—the classical European type transmitted from man to man by lice, and the murine variety spoken of as the Mexican "tabardillo," which is carried to man from a reservoir in rats by the rat flea. Rat lice were also found capable of harboring the virus.

As a result of our work, it has been shown that Brill's disease, heretofore regarded by certain observers as belonging to the murine type, is without question to be identified with the classical European variety of typhus. The interepidemic reservoir of the virus of Brill's disease, however, is still unknown. An epidemiologic analysis of 538 cases of this infection indicated that the virus may be maintained for long periods in a certain small percentage of those who recover. At some later time, recrudescences resulting in clinical cases of disease may occur. Under suitable conditions, these can form the foci for further spread of the infection.

Through the development of a technic involving the lowering of the resistance of rats to the typhus organism by means of x-ray radiation, very large quantities of rickettsiae of the murine type were secured. With this material, immunologic studies showed that it is possible to immunize actively with killed virus. This observation led to the production of a vaccine, which is now being employed as a prophylactic in human beings, and as a means of producing an antiserum in horses. The serum has been shown to contain protective substances against the virus, and will prevent the development of symptoms in guinea pigs if given within three days following infection. By means of this serum, analyses have been made of the immunologic relations between rickettsiae obtained from the European and murine types. These indicate the presence of a common antigenic factor, as well as the possession of a specific character by each. Thus, although antiserum prepared against the murine antigen under special conditions may reveal some protective action against the European infection, its effect is at best only feeble.

Further efforts, therefore, have lately been aimed at the production of large amounts of rickettsiae of the European type for the purpose of producing homologous vaccines and perhaps homologous immune horse serums. The methods used for the production of massive quantities of the murine type of rickettsia proved ineffective. In consequence, attention is being directed to the perfection of tissue culture technic with the purpose of developing a means of obtaining sufficiently heavy growth of rickettsiae to form the basis for an efficient vaccine.

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IMMUNOLOGIC APPLICATION OF PLACENTAL EXTRACT*

Abstract

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THE development of placental extract for immunologic use is the outgrowth of a search for a more satisfactory method of controlling measles. The use of convalescent serum in children exposed to measles dates from the observations of Nicolle and Conseil in 1918. Certain hospitals have for a number of years used convalescent serum effectively in the control of measles. However, even in hospitals, the use of convalescent serum has been limited by the lack of adequate supply; and control of measles by this means in the general population has proved almost entirely impracticable.

Adult immune serum and adult whole blood have been used as substitutes for convalescent serum on the basis that adults who have experienced the disease retain antibodies capable of protecting other persons. The dosage of adult serum must be much larger than that of convalescent serum (15 cc. of adult serum or 30 cc. of adult whole blood, as opposed to 4 or 5 cc. of convalescent serum). The results are less certain than when convalescent serum is used but are sufficiently good to warrant the practice when other means are lacking.

The results with the use of adult serum have led to the general acceptance of the observation that the blood, and possibly the tissues, of most urban adults contains the protective antibodies. Furthermore, if the mothers are immune, infants during the early months of their lives are also immune to measles, apparently by reason of the passage of antibodies from mother to fetus through the placenta. In addition to measles the newborn infant is usually immune to poliomyelitis, scarlet fever, diphtheria and certain other diseases. The actual presence in the umbilical cord blood of the immune bodies to these diseases has been amply demonstrated. These observations have formed the background of investigations into the use of the human placenta and the blood contained in it as a source of antibodies against measles and possibly against other diseases to which newborn infants are immune.

Various methods of preparation of placental extract have been tried, numerous laboratory tests have been made, and clinical trials of the antibody solutions have been conducted over a period of four years. The investigations have now progressed to the point where it may be said that placental extract can be prepared on a large scale furnishing an extensive source of measles serum in the form of human immune globulins for use in the prevention or modification of the disease, and that, at the moment, placental extract appears to be the best material for use in the control of outbreaks of measles in institutions. The control of the disease in the community by placental extract is possible but does not represent the optimal method; obviously, a means of active immunization without the necessity of the patient developing even the mild acute symptoms would be more satisfactory.

The dosage of placental extract, as well as that of convalescent serum or adult blood, is influenced by several factors, notably potency, time of administration, age and size of the patient, and degree of exposure. The only direct method of determining the potency of placental extract has proved to be to test each lot for its ability to prevent measles. The time of the administration is undoubtedly important in determining whether prevention or modification will ensue. Larger doses of extract or convalescent serum may offset, to some extent, late administration, but after the appearance of the rash no effect of the antibodies can be observed. Another factor is the age and weight of the patient, for in general, larger children require larger doses of serum to insure reasonably efficient passive immunization. A factor of some importance is the degree of exposure. It is well established that infection occurs much less frequently in children exposed in institutions than in those exposed to a brother or sister in the home. The economic status of the home is also important, as exposure in crowded homes is especially intimate and, therefore, more likely to give rise to infection.

The administration of placental extract intramuscularly is followed in some instances by local or general reactions; only 6 per cent of patients suffered a local reaction that was classed as moderately severe, and in only 3.1 per cent did the temperature go above 101°F.

Injections of placental extract have not been found to sensitize to subsequent injections of the material. A number of patients have received two or more injections at intervals varying from a few weeks to several months; in no instance were the second or subsequent injections followed by local reactions of more se-

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verity than were observed after the first injection, and in no instance were there any manifestations of specific sensitization.

Immunity following the injection of placental extract, like that following the use of convalescent serum, is passive in type and of short duration. Observations on fifty-four children re-exposed to measles within a few weeks after receiving placental extract indicate that the immunity resulting from the injection is insufficient to protect against re-exposure occurring more than 2 weeks after the administration of the protective dose and that seldom does even modification occur if re-exposure is more than 3 or 4 weeks after the injection. A certain amount of measles antibody may be absorbed from the gastrointestinal tract to bring about a definite passive immunity in some individuals. The oral administration seemed to be more effective in children than in adults.

THE EPIDEMIOLOGY OF INFLUENZA

BY WILSON G. SMILLIE, M.D.*

THE etiologic agent of human epidemic influenza has been determined beyond a reasonable doubt. It is a filtrable virus.

One of the first hints that the acute respiratory infections might be caused by a filtrable virus came from Foster[1] in 1915, working in Dr. Rosenau's laboratory. He infected a volunteer group of soldiers with a filtrate of nasal washings from an acute case of coryza and produced typical symptoms of an acute cold in these subjects. His work was not substantiated for many years.

Shope,[2] working with Dr. Theobald Smith, was studying "mad itch" in cattle on the farms of Iowa in 1931. In the course of his field work he encountered an epidemic of influenza of pigs. He determined that this infection was caused by a filtrable virus. A Pfeiffer bacillus (*Haemophilus influenzae suis*) was also encountered in the lungs of the infected animals, and played an important part in the pathology of the disease. Experimental evidence showed that the Pfeiffer bacillus alone did not produce the infection. The virus alone produced a mild symptomatology, but when the two were inoculated in conjunction, a severe, rapidly spreading, often fatal infection was produced.

In 1932 Smith, Andrewes and Laidlaw[3] in England were carrying out an extensive series of studies on dog distemper. The ferret was utilized for these studies, as it is highly susceptible to this disease. Since the epidemiology and clinical characteristics of dog distemper resemble human influenza to some degree, it occurred to these workers that the ferret might be susceptible to human influenza. The experiment was tried and was successful. Filtrates from the nasopharyngeal secretions of an acute case of typical epidemic influenza, when inoculated by the intranasal route into susceptible ferrets, will produce an acute, severe, though not fatal, upper respiratory infection.

Francis[4] in the Rockefeller Institute in New York carried this work a step farther. He found that the influenza virus, after it had passed through several series of ferrets, then became highly pathogenic for certain species of young mice.

The establishment of these facts and the development of these technics have resulted in a rapid advance of our knowledge concerning the whole field of the acute respiratory infections, particularly epidemic influenza. I shall give no more than a brief summary of the results that have been obtained during the past 2 to 3 years.

Shope[5] determined that the virus of hog influenza was readily transmitted to ferrets. Infection with this virus resulted in a strong immunity in the recovered animals—both ferrets and pigs. He also succeeded in transmitting this virus to mice by intranasal inoculation.

Francis obtained influenza virus from an epidemic that occurred in Porto Rico in 1933. This virus, Porto Rico 8, and the W. S. virus of Andrewes, together with the Shope swine influenza virus, are the standards upon which most of the subsequent work has been based.

CHARACTERISTICS OF INFLUENZA VIRUS

Animals—mice, ferrets and hogs—may be infected only by the intranasal route. Intraperitoneal, subcutaneous and intracerebral inoculations do not produce infection. The virus is relatively large in size, 80 to 120 μμ. The clinical and pathologic picture of the disease in animals is characteristic. The disease has an acute onset with a short incubation period. A high fever is produced, with extensive congestion of the mucous membranes of the upper respiratory passages. The mice and also the ferrets show an extensive consolidation in the lungs. The swine virus is highly fatal to both ferrets and mice. Human virus is highly fatal to mice, but ferrets are less susceptible and usually recover.

The virus is present in human beings only during the early stages of infection and is found only in the respiratory passages. Andrewes reports finding virus as late as the fourth day after onset. In animals the virus is found only in the respiratory passages, including the lungs. The workers have had no success in infecting ferrets with filtrates from cases of sporadic in-

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fluenza or from filtrates of persons suffering with coryza. In other words, the virus has been obtained only from epidemic sources of typical influenza.

The virus has been obtained from sources as wide apart as Alaska, Australia, England, Philadelphia, Boston and Puerto Rico. Immunologic experiments indicate a very close relation, if not identity, between all the various strains that have been isolated.

Furthermore, the relation of human to swine influenza virus is close. Ferrets that have recovered from inoculation with human influenza virus possess a high degree of immunity to the swine virus and vice versa.

Laidlaw[6] has offered the most interesting suggestion that the swine strain of influenza virus may represent the residue of the virus of the great pandemic of 1918, which has become adapted to the pig and has persisted in these animals since the pandemic. This is in accordance with the belief of veterinarians in the Western states, who assert that epidemics of influenza in pigs were unknown until the pandemic of human influenza in 1918. At this time the disease appeared in pigs and has persisted until the present time.

HUMAN IMMUNITY TO INFLUENZA VIRUS

The virus diseases are, in the main, characterized by a solid and lasting immunity following recovery from infection. But influenza virus seems to be an exception. The epidemiologic evidence that was obtained during and after the 1918 pandemic indicated that acquired immunity to epidemic influenza was of short duration. When the disease returned to a given community in 1920, persons who had had influenza in 1918 were attacked in equal or greater numbers than those persons who had remained free from infection in 1918.

Ferrets are highly resistant to reinfection with influenza virus for a period of 3 to 6 months after recovery from their initial infection. After a period of 6 to 7 months has passed, immunity begins to wane. A single subcutaneous injection of living virus in ferrets at this time, though producing no symptoms, will again produce complete immunity against reinfection by the intranasal route. Furthermore, subcutaneous or intramuscular injections of living virus in mice, ferrets and swine, if given in three doses at weekly intervals, will produce a high degree of immunity against subsequent infection by intranasal inoculations with influenza virus.

Francis and Magill[7] have vaccinated a group of human volunteers with living tissue culture virus of human influenza. Three subcutaneous injections were given at weekly intervals. No constitutional symptoms were produced. In every instance a marked and rapid increase in virus-neutralizing serum antibodies was determined by mouse protection tests.

Laidlaw and his co-workers,[8] by subcutaneous inoculation of living virus into horses, have produced a hyperimmune serum which has great protective value to inoculated mice. Some degree of therapeutic efficacy was observed, even when the serum was given 72 hours after the mice had been infected. There are no reports as yet concerning the results that may be secured by treatment of human influenza patients with this hyperimmune serum.

THE NEUTRALIZATION OF INFLUENZA VIRUS BY HUMAN SERUM

The presence of neutralizing bodies to influenza virus in human blood may be determined quantitatively by standard mouse protection tests. Blood that is withdrawn from an individual during the early stages of infection with epidemic influenza does not neutralize virus P.R. No. 8. Protective bodies appear in the blood during convalescence, and persist. No increase of these protective bodies in human serum occurs subsequent to an attack of coryza, even though the attack be a severe one. Francis and Magill[9] made observations also upon a series of cases of lobar pneumonia to determine if these individuals developed immune bodies against influenza virus. In their study there was an increase of protective bodies against influenza virus in only one instance. The history of this patient suggested that the individual was suffering with an attack of influenza which had been followed by lobar pneumonia.

Many normal individuals possess protective bodies in their blood against influenza virus P.R. No. 8. Furthermore, many persons possess immune bodies against the virus of swine influenza. This is particularly true in adults. Laidlaw showed that protective bodies against swine influenza virus are rarely, if ever, encountered in children under 10 or even 15 years of age; whereas children from 5 to 10 years of age frequently possess immunity against the W.S. or P.R. No. 8 strains. This is one of his reasons for suggesting that swine virus is a residual of the strain that produced the epidemic of 1918.

Brown,[10] working in the Harvard School of Public Health in 1936, tested the serums of 30 adults who had had influenza during the 1918 pandemic. The serums of 8 persons completely neutralized the P.R. No. 8 virus; the serums of 15 possessed moderate protective powers; and the blood of the remaining 7 contained no demonstrable antibodies. This result is almost identical with that obtained in Laidlaw's series of 29 adults. Laidlaw's group, however, was selected without reference to past history of influenza.

Brown studied 3 adults who did not develop influenza in 1918 or subsequently. Two others escaped influenza in 1918, but gave a history of influenza in recent years. All 5 possessed strong protective power against the P.R. No. 8 strain.

In a study of 32 children Brown found that infants and very young children possess little immunity against human influenza virus. Immune bodies are rapidly acquired after the age of 3 years, and children of 15 years of age possess almost the same degree of immunity as adults.

The 35 adults that were tested in Brown's series had recently arrived in Boston from all parts of the United States and from such distant parts of the world as Esthonia, Japan, Chile, Albania, Rumania, China and Argentina. The majority of these adults from all these various regions possessed immunity against the P.R. No. 8 virus.

One epidemiologic conclusion seems clear-cut. There must be a highly prevalent influenza virus that is spread to all parts of the world. This virus must be closely related antigenically to the W.S. virus of Andrewes and the P.R. No. 8 virus of Francis. The whole community must be exposed to this virus at fairly frequent intervals from early childhood. Certainly, children of 3 years of age and older rapidly build up an immunity against this infectious agent, so that when adult life is reached most persons possess some protection and some have a high degree of immunity.

We may surmise that exposure to this virus on the part of those of us who possess some degree of immunity may result in a mild infection which might be mistaken for a common cold. Yet this mild infection may rapidly build up the infected individual's resistance to the influenza virus to a high degree. This is exactly what happens in laboratory animals.

What are the relations of colds, of grippe and of sporadic influenza to epidemic influenza?

Acute respiratory infections are now classified on a clinical basis. The diseases are given different names in accordance with the severity of symptoms. Past experience with other types of acute infection indicates clearly that when the etiologic agent of a disease has been discovered, differential diagnosis is rapidly clarified and actual conditions determined on the basis of the etiologic agent. It is quite possible that all the virus infections of the upper respiratory tract are closely related and differ only in the degree to which they affect the individual. Thus we were able to show that an epidemic of acute respiratory disease in an isolated community in Labrador produced all degrees of illness in the small population. The symptomatology ranged from that of a simple cold to the most severe type of typical influenza. The only contact of this community with the outside world was a dog-team driver who brought in the infection from a post 100 miles away.

The evidence so far accumulated in relation to epidemic influenza, however, suggests that the disease is a separate clinical entity with specific etiology. In Brown's study there were several persons whose serum titers against influenza virus P.R. No. 8 had been recently determined. Subsequently, these men developed illnesses that were diagnosed as grippe or as influenza. Brown found no increased protective power in their blood against the P.R. No. 8 virus following their illness.

A recent observation of Wells and Brown[11] in the Harvard School of Public Health in relation to possible mode of spread of influenza is interesting. They showed that when the virus of influenza was sprayed into the air of a glass-lined tank, the virus was widely dispersed through the air and remained suspended in the air of the tank for at least 2 hours. They also showed that when this infected air was exposed to ultraviolet light, the virus was destroyed almost instantly. This observation may have great practical significance in the whole field of air sanitation. Engineers are already giving consideration to the proper equipment for installation of ultraviolet light in the air-conditioning equipment of operating rooms, hospitals, theaters and other places of public congregation.

SUMMARY

The virus of epidemic influenza is widely distributed. All the strains isolated thus far are closely related antigenically. Infection with the virus produces a high degree of immunity, which is apparently of short duration. There is some evidence that the specific immunity in human beings following an attack of influenza largely disappears in 2 years. In animals this lost immunity can be rapidly regained by a single subcutaneous injection of living virus. These results have led workers in this field to hope that it may be possible to produce artificially an active immunity in human beings against the virus of epidemic influenza. It seems probable that such an immunity would be of short duration, but that it might be renewed by appropriate means.

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THE IMMUNE REACTIONS IN PATIENTS WITH GONOCOCCAL INFECTIONS*

BY CHESTER S. KEEFER, M.D.,† AND WESLEY W. SPINK, M.D.†

FOR several years we have been engaged in the study of the immunologic reactions that occur during and following gonococcal infections. Our particular interest in this subject has been stimulated as a part of a general investigation of arthritis. In the case of gonococcal arthritis, the cause is known. The inflammation begins in the periarticular tissues and the synovial membrane and, in this respect at least, resembles other types of arthritis in which the cause remains obscure. By studying this disease intensively and by gathering more precise information regarding the factors influencing the localization of infection and the mode of recovery, it is not unreasonable to suppose that one may be able to obtain additional facts concerning diseases of the joints in general.

It will be conceded generally that some of the more important questions to be answered in studying any infection are: (1) What is the mode of invasion? (2) What are the factors which immobilize organisms, suppress their multiplication, and finally destroy them within the host? In the infection under discussion, the mode of infection and its spread are well-known. The other questions mentioned are not very well understood, and our experiments were planned to throw more light upon them.

In previous studies, the clinical course of patients with gonococcal arthritis was presented, the characteristics of the synovial fluid defined, and the factors bearing on prognosis tentatively outlined. At present, we submit the results of our investigations that deal with the matter of the immunologic response on the part of the host following invasion by the gonococcus. Inasmuch as our time is limited, we shall not describe the details of the methods of study that were used. They will be published shortly in a full report.

The first problem dealt with the method of destruction of the organism in vitro. The relative importance of plasma or serum and the leukocytes was investigated. It was found that the gonococcus was destroyed in vitro by the process of lysis. This was accomplished by the action of complement on sensitized bacteria. There was no evidence that the leukocytes destroyed these organisms by intracellular digestion as is the case in infections caused by gram-positive bacteria; and, indeed, we were unable to obtain any evidence that the phagocytosis of organisms by leukocytes was of any aid in their destruction in vitro. Additional experiments demonstrated the fact that the bacteriolytic power of the blood could be enhanced by the addition of immune serum to whole blood in vitro, and following its exhibition to patients.

Having learned that the organisms were destroyed in vitro by lysis, the next step was to determine the bacteriolytic titer of the blood from noninfected individuals and from a group of patients with gonococcal infection. These patients included those with local lesions and those with arthritis. The method employed was the one developed in Doctor Zinsser's laboratory by Doctor Ward for the study of the bactericidal action of the blood for the pneumococcus. Whole defibrinated blood was used, and the maximum number of gonococci that could be killed in 0.5 cc. of blood determined. Several hundreds of tests have been carried out on a series of 29 patients.

In a word, it was clearly evident that the blood from noninfected individuals was capable of killing varying numbers of gonococci, depending upon the strain that was employed in the test. There was very little difference in the killing power of various individuals for the same strain. It was more common to find a lower bacteriolytic titer for strains of gonococci obtained from arthritis than for strains derived from urethritis. This was taken to be suggestive evidence of the difference in the invasive properties of the various strains of gonococci, as well as differences in the natural bacteriolysins in noninfected individuals.

With a few exceptions it was common to find an increase in the bacteriolytic titer of the whole blood during the course of gonococcal infection. This was found more often in patients with arthritis than in those with local infections. If we assume that sensitizing antibodies are significant, it did not seem unlikely that the appearance or increase of bacteriolysins was of importance in destroying the gonococcus, although the relative importance of these bodies in the whole recovery mechanism could not be assessed from these studies alone.

We then turned our attention to a comparative study of the antibody content of synovial fluid and blood derived from the same patient. From previous studies of synovial fluid in gonococcal arthritis there was a fair body of evidence to indicate that such fluid consisted mainly of an exudation of blood plasma with the

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addition of mucin and a large number of leukocytes. It did not seem improbable, then, that bacteriolysins would be detected in the synovial fluid. It was ascertained that they were present either in the same or in smaller amounts than exist in the blood plasma. When the fluid was sterile, the bactericidal titer was commonly the same as that of the blood; when the fluid was infected, the antibody content was usually less than that of the blood, although antibodies could be demonstrated.

In seeking an explanation for the difference between the synovial fluid and blood, we investigated the effect of mucin on the bactericidal action of whole blood and immune serum containing antibody. It is well recognized that the gonococcus usually begins its invasion of the host upon a surface of the mucous membrane where there is an abundant supply of mucus, and that once the gonococcus invades the body from its portal of entry it localizes and multiplies in the joints and tendon sheaths, which are supplied by mucus. It was suggested, then, that mucin might favor the growth of gonococci. We were unable to convince ourselves that mucin alone supported the continuous growth of organisms in vitro for a period of more than 28 hours. With a few exceptions, the addition of mucin to whole blood containing bacteriolysins was followed by a reduction of the bacteriolytic power. In some, the bactericidal action of the blood continued to be operative in the presence of mucin. This inhibition of the action of antibody was not because of a decrease in the complement, but in some way interfered with the sensitization of the organisms. We have had an opportunity of making similar observations in vivo. Large amounts of antibody were injected into the knee joint of a patient who had an infected fluid. As long as there were large amounts of mucin present it was not possible to sterilize the cavity in this way. In the face of the above facts, it can be reasonably maintained that mucin aids organisms in their struggle with the host. These observations assist one in understanding the reason for the survival of organisms in an environment which is supplied by mucin, even when antibodies can be demonstrated to exist.

In view of our observations that the gonococcus is killed in vitro by lysis and that the addition of antigonococcal immune serum enhances the bacteriolytic titer of the blood both in vitro and in vivo, we had an opportunity of using this information in a practical way in a patient with gonococcal bacteremia and chronic gonococcal prostatitis. This blood serum infection was accompanied by a symptomatic purpura hemorrhagica, hepatomegaly and splenomegaly with jaundice. The bactericidal power of the blood was low, but it was effectively increased and the blood was sterilized following the injection of antigonococcal serum.

From our experiments and observations so far, we are justified in making the following statements.

The gonococcus is killed in vitro by lysis. This is accomplished by a sensitization of the organisms by antibody, and their destruction is completed by complement. There is no evidence that phagocytosis of organisms is important in this process. Different strains vary in their invasive properties, and this is dependent, in part, upon the presence of natural bacteriolysins and, in part, upon the ability of the gonococci to survive in areas abundantly supplied with mucus.

During and following a gonococcal infection, the bacteriolysin titer of the blood increases. This is seen more often when there are metastatic lesions, such as arthritis.

A study of the bactericidal content of synovial fluid indicates that it may be the same as the blood when the fluid is sterile and that it may be lower when the fluid is infected.

The presence of mucin may reduce but does not abolish the action of antibody. This is not caused by an alteration of the complement titer of the plasma or synovial fluid. There is some evidence that it interferes with the sensitization of organisms.

The addition of antigonococcal serum to blood in vitro and in vivo increases the bacteriolytic titer of the serum. This is of some practical importance in gonococcal bacteremia without endocarditis.

IMMUNIZATION IN YELLOW FEVER AND OTHER VIRUS DISEASES*

BY ANDREW WATSON SELLARDS, M.D.†

IT is refreshing to see today that there are still many people interested in infectious diseases though many of you may doubt very much that there can remain anything of interest concerning yellow fever. It was considered to be a dying disease about 20 years ago. A commission was formed for its complete eradication, and some of the members could hardly wait to begin work for fear the disease would just van-

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ish before they could make a start. The epidemiology is better understood now. Yellow fever is firmly established endemically in South America and in Africa. Indeed, the development of colonial empires in Africa requires the opening up of the continent with roads and good communications. This in itself might be sufficient to permit yellow fever to flare up extensively and it is necessary to take precautions against such an accident.

Occasionally some of my friends here ask me whether yellow fever is an insect-borne disease. Well, to go back to 1900, the United States Army Commission in Cuba followed up the excellent lead of Finlay and proved the role of the mosquito.[1] They also established clearly that the virus of yellow fever is easily filtrable and this was fully confirmed by the French Commission in Rio de Janeiro.[2] The filtrability of the virus was rediscovered recently in studies on monkeys. Moreover, the Army Commission considered that the specific etiology is quite unknown and this conclusion remains true today. The interest that once centered in *Leptospira icteroides* has disappeared, for we have demonstrated that this organism bears no relation to yellow fever and that it is identical with the leptospira which causes a totally different infection, namely Weil's disease (leptospiral jaundice).[3] These results rendered quite clear the necessity in the study of yellow fever of searching anew for an experimental animal of suitable susceptibility.

Activity in the study of yellow fever falls quite naturally into three periods. The first one includes observations of distinct importance made before 1900, that is, before the discovery of transmission by the mosquito (*Aëdes aegypti*). The second is from 1900 to 1928 when experiments were made exclusively on human volunteers. The third period began in 1928, when Stokes and his associates[4] of the Rockefeller Foundation learned that the ordinary Indian monkey (*Macacus rhesus*) is extremely susceptible to infection. Ordinarily the monkey develops fever and jaundice, the course is rapidly fatal and the liver shows widespread necrosis. Very often the liver dies some hours before the monkey dies.

It was by reason of the very generous and continuous cooperation of the French authorities in their Pasteur Institutes in Paris and in their African colonies that we were able to study yellow fever. In 1928, Mathis, Laigret and I[5] obtained a very satisfactory strain of virus in Senegal. A simple and safe method was found for the preservation and the transportation of the virus in vitro and this was the first strain to be taken out of Africa.[6] It was established at once in several laboratories in Europe, and also in London, in New York City and here in Boston. At first glance it may seem unnatural to attempt such work so far from the home of the disease, but it is vastly easier to keep the virus under control in this climate than in endemic zones where susceptible mosquitoes may be flying about. As an initial step, we found no evidence for the suggestion, which had been offered rather freely, that yellow fever as it occurs in Africa might be a separate entity quite distinct from the disease known as yellow fever in America. Dr. Tyzzer noted that the pathologic lesions were identical in autopsy material that we had collected in South America and in Africa. Furthermore, we found that the serum of convalescent patients in Brazil protected monkeys against the strain of virus from French West Africa.[7]

Theiler,[8] working here in this building, injected the virus into the brains of ordinary white mice. Almost every mouse that was injected died of encephalitis, with no jaundice and no lesions of the liver. After many passages through the brains of mice, a neurotropic strain of the virus was developed. This seems improbable enough, but I wish that you would follow closely this next part because it does not even sound possible. We were much surprised to find that the injection of infective mouse brain into the brain of a monkey produced a fatal encephalitis, but with no jaundice and no lesions of the liver.[9] This is a quite artificial disease; as far as we know at present, it does not exist in nature, and that is a mercy. Moreover, at least for practical purposes, the neurotropic strain of the virus is not transmitted by the mosquito, *Aëdes aegypti*, a species that is extremely susceptible to the virus of yellow fever in its ordinary form. Now we come to a very practical point. Injection of the neurotropic virus, not into the brain, but under the skin of a monkey, produces almost no reaction, but the animal becomes solidly immune against yellow fever in any form. I do not like such sweeping assertions, but believe that this one is fundamentally sound. These observations on the neurotropic strain of yellow fever have been confirmed in other institutions.

With this information and with a very kindly reception from Professor Roux in Paris, we undertook in Africa the application of this technic in man. Laigret and I injected the living neurotropic virus subcutaneously and the first results were favorable.[10]

The test of the effect of neurotropic virus was approached with care. As a precautionary measure, two injections of killed virus were given. No demonstrable antibodies developed, and this practice was discontinued. The measurement of minute amounts of living virus was effected by titrations in mice. Tenfold dilutions of infective mouse brain were prepared and, after centrifugalizing out the brain tissue,

the supernatant fluid was injected in amounts of about 0.03 cc. into the brains of mice, using a group of six animals for each dilution. With the strain of virus in use at this time, a dilution of 1 to 10,000 was just sufficient to kill the mice with regularity. Accordingly 0.5 cc. of a dilution of 1 to 1,000,000 was chosen for the first injection in man. Subsequently 1 cc. of a 1 to 10,000 dilution was tested. Eventually, a dilution of 1 to 100 was used in one instance, but this resulted in a slight bradycardia with the appearance of a trace of albumin in the urine without subjective symptoms. Accordingly, we have at all times insisted on the employment of only minimal amounts of virus, especially as we noted in our first tests that an infinitesimal quantity was sufficient to produce immunity in man. Although there was a persistent demand for a vaccine for yellow fever, Laigret spent 2 years in developing the method of immunization in order to make a prudent and cautious transition from an experimental to a practical basis. The employment of this technic was recommended only after it had been subjected to an extensive practical test, which Laigret accomplished successfully in the summer of 1934, when he returned to Senegal with this much modified strain and vaccinated more than 3000 volunteers.[11]

Now every new vaccine or serum for any disease usually starts off beautifully, and all of you know without asking that not one of the vaccinated persons has ever developed yellow fever. Sometimes one small precise experiment is of value in the interpretation of a considerable amount of probable evidence. The serums of the vaccinated persons show a high protective titer for animals. But Aycock[12] has demonstrated that monkeys may be quite susceptible to poliomyelitis even though their serums possess good neutralizing properties. The following observations were made by Laigret and me.[13] One of the men on the staff, familiar with every detail of the experiment, was given one immunizing injection of neurotropic yellow fever virus, using 0.5 cc. of the supernatant fluid of a 1 to 1,000,000 suspension of infective mouse brain. This represented approximately 15 mouse units of virus. We proved in the laboratory that an infection occurred, but it was almost inapparent. The temperature rose on the sixth day to nearly 100° F. but with practically no subjective symptoms. Subsequently, protective properties of the serum were readily demonstrated, using mice for the neurotropic strain and monkeys for the ordinary virus of yellow fever. This serum, however, failed to give any protection when injected in mice together with yellow fever virus in its ordinary form. This test was made by intracerebral injection, and the failure was clearly caused by the use of an excessive dosage of virus. Infectious monkey serum was employed in a dilution of 1 to 1000, and a titration showed eventually that a dilution of at least 1 to 100,000 would have been more appropriate, since all of the mice injected with this minimal amount of infectious blood died of encephalitis. This failure of protection in the presence of a known immune serum merely emphasizes the inherent neurotropic property of the ordinary virus of yellow fever. Seven and three-fourths months after the immunizing injection, the subject was bitten by infected mosquitoes, and there was no reaction whatever. Two monkeys that were bitten by the same mosquitoes died typically of yellow fever. So much for the efficacy of the procedure.

There are some definite dangers to be recognized. Twenty thousand persons have been vaccinated and there have been four or five who showed serious meningeal reactions. Fortunately all of these terminated in complete recovery. It may prove a difficult task to find some method of avoiding these rare but very severe reactions.

Sawyer and his associates[14] introduced serovaccination primarily for the purpose of interrupting a long series of accidental infections, which had occurred in laboratory workers. We have not practiced vaccination of the laboratory personnel, and we are concerned chiefly with methods that are applicable in the protection of communities. Serovaccination involves the injection of a limited amount of immune serum and a substantial quantity of living neurotropic virus (approximately 0.05 gm. of infective mouse brain, less the amount lost by filtration). Thus for serovaccination one infective mouse brain would furnish sufficient virus for about ten persons; for vaccination without serum one mouse brain would furnish sufficient virus for about 1,000,000 people, according to the dosage used in the experimental case that we have just described. Serovaccination involves the use of an amount of immune serum small enough to permit a transient infection but sufficient in quantity to prevent the circulation of any virus in the blood stream. In their original report, Sawyer and his associates described the vaccination of sixteen individuals by this method. They presented evidence that the amount of immune serum that was injected did not produce a passive immunity but that it localized the infection. Five of these sixteen cases were examined, and no virus was recovered from the circulating blood. However, three of these five cases were tested not later than one to three days after their injection, a period of time that is several days in advance of the expiration of the period of incubation. Several hundred persons have been treated by serovaccination. Following their own technic in the Pasteur Institute, one instance has been reported of serious involvement of the central nervous system, terminating in complete recovery without sequelae.[15]

There is a growing tendency to require methods of immunization that are absolutely without

risk, that cause no inconvenience and that provide complete protection against dangerous diseases. These desiderata have not been achieved completely for yellow fever, for smallpox or for rabies, three diseases in which modified living viruses are used for protective inoculation. At first glance, it would seem that, if a virus is dangerous in large doses, then it could not be used at all with any degree of safety; but one comes to consider, perhaps with some reluctance, that minute doses of living virus are reasonably safe in certain cases. In rabies and in our own method for yellow fever we insist on the use of minimal amounts of virus. For smallpox, vaccinia virus is commonly used more or less ad libitum because for mass vaccination we hope that one inoculation will give effective protection. However, for the individual patient, I would like to see a more gradual approach. There is just a possibility that the use of smaller amounts of virus and attention to other details might render some of the accidents less frequent.

With the lapse of years since the introduction of rabies prophylaxis, it is natural to assume that a decision would have been reached concerning the best method of treatment with an explanation of just how it works. On closer examination we find that we are somewhat in the dark on both of these points. Of the many methods of treatment, there is one very radical departure from the technic of Pasteur, perhaps too radical, namely the use of killed virus, as commonly employed in this country. For myself, if I had the misfortune to meet a mad dog, I would be quite uneasy for many, many months unless some form of living virus were available for treatment. However, this feeling cannot be supported by actual figures. In the analysis of approximately 500,000 cases, McKendrick[16] was unable to detect any differences of statistical significance in the mortality rates following treatment with living virus as compared with the use of killed vaccine. Regardless of the type of treatment, the mortality rates are extremely low (about 0.25 to 0.5 per cent), and the decision concerning the treatment of choice may very likely have to be reached in some way other than by the statistical method. In the meantime, when one sees or hears of a few patients treated with killed virus and subsequently rabies develops, it might make one wish that one had used some form of the original Pasteur treatment. My interpretation would be that living virus represents the conservative form of treatment and that the use of dead virus is rather radical. The procedure of choice may ultimately prove to be some form of combined treatment. Thus, in his original method, Pasteur followed the prudent plan of commencing the injections with killed virus and completing the immunization with increasing doses of living virus.

The point about the theoretical explanation is not very tedious. I took pains to talk this over with Dr. Hornus, a visitor here from the Pasteur Institute of Paris. Dr. Hornus assures me that we do not know the fate of the fixed virus of rabies when it is injected into a patient. The virus may be killed promptly by the tissues or it may multiply and give rise to an inapparent infection. However, experimental attempts to recover fixed virus from animals undergoing Pasteur treatment have almost always failed.[17] The idea of an inapparent infection would fit exactly with our present-day conception of immunity in virus diseases. If a mild infection occurs, then we would want to find out whether the subsequent long course of daily injections of virus is advisable. We must wait for the final explanation. In the meantime, it is necessary to continue the daily injections and we may feel confident that the intuition of Pasteur was remarkably accurate.

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THE ANTISERUM TREATMENT OF PNEUMONIA FROM THE STANDPOINT OF PUBLIC HEALTH

BY ELLIOTT S. ROBINSON, M.D.*

PNEUMONIA, which ranks third as a cause of death in this country, belongs to the group of diseases which are not susceptible to elimination either by sanitary engineering methods, as is typhoid, or by mass immunization, as is diphtheria. Our present knowledge does not permit us to do more than attempt to decrease the death rate by prompt and adequate treatment of such cases as are amenable to specific serum therapy.

The studies at the Rockefeller Hospital by the group under Dr. Rufus Cole demonstrated 20 years ago that certain cases of pneumonia—those caused by the type I pneumococcus—yielded to treatment with antiserum. Because of the large doses of serum required, this method of treatment, in spite of its efficacy, was little used outside of the larger hospitals. Moreover, since less than a third of the cases of lobar pneumonia are caused by this type of pneumococcus, this form of therapy was by no means generally applicable.

In 1924 Felton announced his success in concentrating antipneumococcic serum. As a result of this and of his improvements in methods of determining the strength of such serums, it became possible to prepare serums of known potency, and of such concentration that adequate doses could be given in reasonably small volumes. This work revived the waning interest in antipneumococcic serum therapy and led to study of serums for type II pneumococci as well.

The success of Felton's work led us to the belief that serum therapy could and should be tried on a much larger scale than had been previously attempted. We felt that as long as serum therapy was confined to the larger hospitals, much of its usefulness was being lost, for relatively few cases reached such institutions, and of those that did, a proportion had passed the period at which serum therapy is most successful. Moreover, no proper evaluation of serum therapy could be made except on the basis of a study of larger scope than any which had been attempted up to that time (1930). The Massachusetts Department of Public Health therefore evolved a plan for the use of serum on a statewide basis and obtained money from the Commonwealth Fund of New York City for this purpose. The essential features of this plan and the attainments of its execution can be described together.

1. Because no benefit is obtained by treatment with serum of the wrong type, the serologic type of pneumococcus involved in each and every case must be determined as promptly as possible. Although in the beginning of the study serum was administered before typing was done, it is now feasible to insist upon typing before the institution of serum treatment, thanks to the development of more rapid methods of typing than were available in 1931. To insure prompt and accurate typing, approximately seventy laboratories in all parts of the State are now available at which typings are done. In many of these laboratories, the technicians have received training in this procedure at the State Diagnostic Laboratory.

2. As is true of most serum therapy, the early exhibition of antipneumococcic serum is of more value than its administration late in the course of the disease. For this reason and also to extend its use to more cases, serum was made available for use at home as well as in hospitals.

3. The serum must be administered intravenously and in rather large doses. It was expected, therefore, that some physicians would hesitate to make use of it. For their assistance, arrangements were made by which they could obtain nearby physicians with special training as consultants. These consultants were compensated by the Fund when the patient was unable to pay for them. The use made of these consultants varied in different areas, but this or some similar arrangement is essential to the introduction of a new and difficult form of therapy.

4. Information about the serum treatment of pneumonia was disseminated by articles in medical journals, by talks at medical society meetings, and by special graduate courses.

5. It is necessary to exercise some central control, preferably by the state health authority, over the amount of serum used per case, in order to keep the cost within reasonable limits. As our experience has increased, it has been possible to classify cases on a basis of age of the patient, duration and extent of the disease and presence of complications in such a way that sufficient but not excessive amounts of serum may be issued for each patient. There are undoubtedly instances in which individuals might suffer from such limitation, but these can be handled individually and additional serum issued on presentation of the circumstances to those in charge of serum distribution.

6. Records of the use of serum must be kept for each case and sent to the health department office for tabulation and study. These records must give sufficient detail to permit drawing conclusions about the efficacy and safety of the

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serums distributed, and to serve as a guide in determining whether present dosage schedules are adequate.

These are to our mind the essential points in employing antipneumococcic serum therapy in a public health program. Beginning in 1931, this plan has been gradually introduced throughout the Commonwealth of Massachusetts and is at present in operation as outlined, except that the consultant service paid by the special fund is no longer available. In the years 1931 to 1935, inclusive, nearly 400 physicians in 98 towns treated 213 patients at their homes and 743 in hospitals, a total of 956. Since the special study was discontinued at the end of 1935 and the work undertaken as a state project, there has been no obvious diminution of interest, and in fact the distribution of serum has shown the normal increase that would be expected as its value became more widely realized.

Not much should be said in regard to cost because relative cost will decrease as more general use is made of serum and its preparation can be conducted on a larger scale. Moreover, increasing knowledge of methods of preparation should tend to lessen the cost of serum production. According to our present ideas of proper dosage and taking into account the occurrence of positive blood cultures—the chief reason for giving more than the minimal dosage—we may figure that type I cases will require an average of 75,000 units, and type II cases about 135,000 units each. At present retail prices, this would amount to about $45 for a type I and about $80 for a type II case; the costs are materially less if serum is supplied under governmental auspices either through purchase by contract or through governmental manufacture. Although these costs are large in comparison with the cost of active immunization against diphtheria, for example, it must be borne in mind that lobar pneumonia is a disease attacking adults in the prime of life and at the threshold of, or actually in, the period of their greatest usefulness. Because of this fact, the cost does not seem excessive.

From such figures as are at hand, one can estimate what might be expected if the serum treatment of pneumonia is generally applied. Realization will fall short of this, for Massachusetts is not yet Utopia and human nature remains human nature; but the estimates may be altered in proportion to our lack of faith. For the 10 years 1921 to 1930, inclusive, there were approximately 48,000 cases of lobar pneumonia and 20,500 deaths reported in Massachusetts. This indicates a fatality rate of 42.5 per cent, which is so much beyond the usual hospital rate of 25 per cent that probably the actual number of cases in that period was not less than 80,000. Of these about 24,000 were probably type I infections, 16,000 type II, and 16,000 types V, VII or VIII, for all of which serum therapy is apparently of value. Of the 24,000 type I cases, probably 6,000 died; of the 16,000 type II, probably 6,400 were fatal; and of the 16,000 of types V, VII or VIII, 4,000 succumbed. We believe that proper serum therapy will reduce the death rate in type I infections from its normal 25 per cent to 10 per cent, which would have meant 2,400 deaths instead of the estimated 6,000 during the 10 year period. For type II infections the respective fatality rates are 40 per cent and 25 per cent, or a reduction from 6,400 deaths to 4,000. For infections due to types V, VII and VIII, we can make no prediction, for too few cases of serum therapy of these types have been recorded. For types I and II together, the estimated possible saving is 6,000 lives for the 10 year period. These figures apply to Massachusetts and are obviously more or less vulnerable to attack, but we believe the figures are representative and the estimates reasonable, especially as our knowledge and, therefore, the efficacy of serum treatment increase.

In closing, I would like to stress the fact that the use of antipneumococcic serum in the public health field is no longer an untried procedure. We, in Massachusetts, know that such serum therapy has a place and will continue to have a place until a better method of treatment, or perhaps of prevention, becomes available. Our belief is strengthened by the recent adoption of plans similar to ours in Connecticut, Maine, New York and Michigan.

SOME ASPECTS OF PNEUMOCOCCUS INFECTION IN MAN*

Abstract

BY MAXWELL FINLAND, M.D.†

IN this paper is presented a résumé of some observations made during the past year with Dr. R. C. Tilghman. They concern chiefly serologic reactions among family contacts of pneumonia patients and bacteriologic studies of the pharyngeal flora of such contacts with respect to the pneumococcus.

A survey of the instances of multiple cases of infection with "typed" pneumococci occurring within a family and treated at the Boston City Hospital led to the following conclusions: (1) The cases within a family are usually

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caused by pneumococci of the same type. (2) Pneumococci of types other than I and II may be responsible for family outbreaks. In particular, instances were encountered of outbreaks of infections due to types V, VII, XII, XIV, and XXII pneumococci. (3) Within a family, the same type of pneumococcus may give rise to lobar pneumonia in one member and to bronchopneumonia or to primary meningitis, otitis media and probably milder upper respiratory tract infections in other members. (4) The time relations among such cases suggest that the causative pneumococcus was derived either from a common source outside the family or from direct contact within the family.

Two instances were presented of pneumonia occurring in the hospital probably as a result of contact with ward patients ill with pneumococcus pneumonia. One was the case of a physician who acquired a type VII pneumococcus pneumonia from a patient whom he was treating; the other was an ambulatory diabetic patient who acquired a fatal type V pneumococcus pneumonia after comparatively brief contact with a fellow patient who had a similar disease.

A study of the pharyngeal flora of family contacts of patients with pneumonia revealed a high incidence of carriers of the same pneumococcus type. Most of these contact carriers were found to have antibody (passive protection for mice) for the same pneumococcus type in titers approaching those encountered in cases recovering from pneumonia. In the contacts who carried types of pneumococci other than the one causing infection in the relative, antibodies for the corresponding types were not found. Occasional instances were observed in which antibodies were first demonstrated after the organism was cultured from the pharynx.

One family was presented in which two consecutive epidemics occurred about 1 month apart. The first involved three members who were sick with type V pneumonia, and the second involved four siblings ill with type XXII pneumococcus infections. The original source of the type XXII epidemic was shown to be a healthy carrier, who was the first member of the family to carry this organism in his pharynx and who, without any evidence of disease, had antibodies in high titer for this type.

The details of these studies have been published elsewhere.[1, 2]

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STUDIES ON FILARIOIDEA*

Summary of Remarks

BY RICHARD P. STRONG, M.D.†

HAVING heard a discussion regarding a number of infectious diseases of bacterial origin, we will now ask you to turn your attention to some problems in parasitology and to consider several infections produced by animal parasites.

The morbid conditions produced by certain parasitic nematodes of the superfamily, Filarioidea, constitute some of the most important problems in tropical medicine and parasitology. These parasites, however, are not only of great interest from a pathological standpoint, but also from a zoological one. They may be classified in two families, the Filariidae and the Dracunculidae. In the Filariidae the females at most are three or four times as long as the males and the vulva is not atrophied in the gravid female, while in the Dracunculidae the females are enormously longer than the males and the vulva and anus are atrophied in the gravid female.

From the table we see that representatives of five of the genera infect man—these species being *Acanthocheilonema perstans* and *ozzardi*, *Loa loa*, *Onchocerca volvulus* and *caecutiens*, *Wuchereria bancrofti*, *Microfilaria malayi* (of which the adult has not yet been described) and *Dracunculus medinensis*.

In man the parasites invade the circulatory or lymphatic systems, the connective or muscular tissues or the serous cavities. The remaining members of the superfamily are parasites of wild or domestic mammals, birds, fish and reptiles, as well as of all other classes of vertebrates.

Apart from the morphologic characters that you had an opportunity of observing at the demonstration in the Department of Tropical Medicine yesterday, the Filariidae possess an important biologic distinction from almost all other nematodes in that in all species whose development is known an intermediate host is required for the larval stages. Part of the development takes place in some bloodsucking insect which transmits the larvae to a fresh host. Thus in *Acanthocheilonema perstans* the transmitting insect is *Culicoides austeni* or *grahami*, while in *Loa loa* it is the mango fly of the genus *Chrysops* (*sp. dimidiatus* or *silacea*). With *Onchocerca volvulus* and *caecutiens*, at least

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five species of *Simulium* are capable of transmitting the infection, while with *Wuchereria bancrofti,* some five genera of mosquitoes may probably serve as the intermediate host—particularly, *Culex fatigans, C. pipiens, Aedes variegatus* and *Anopheles rossi.* With *Microfilaria malayi,* however, certain species of Mansonioides are regarded as the transmitting agent.

In the Dracunculinae there is no insect host, the intermediate host in this instance being a mollusk, *Cyclops.* The female of the species, *Dracunculus medinensis,* the notorious Guinea worm and the reputed fiery serpent of the children of Israel (which measures in the neighborhood of a meter in length), is probably the oldest parasite known, it having been even illustrated as early as 1598 and described as early as 1674 by Velsh. However, the male parasite in the human being has not yet been either definitely seen or described. It is presumed that it disappears soon after impregnating the female. In fact, it is only through the study of other species of *Dracunculus* and *Philometra,* particularly those that invade the lower animals and that infect certain fish and the snapping turtle, that the male of the parasite of this species has been discovered and that the elucidation of the life history and the method of transmission by *Cyclops* has been satisfactorily explained. Thus in *Dracunculus globocephalus,* which infects the snapping turtle, the male parasite has been found by Mackin, and in *Philometra globiceps* which invades the gonads of fish (*Poronotus*) that abound in Woods Hole, Linton, Sandground and others have also found the male. Strassen, Ward and Magrath have made other studies regarding the life history of the parasite in perch and other fish. As, however, you had an opportunity yesterday of observing many of these and other zoological features at the demonstration, I will confine my further remarks to a few pathological and clinical facts regarding several of these parasites.

The adult female *Dracunculus medinensis* is found in the subcutaneous connective tissue in man, and, when gravid, it leads to the formation of superficial ulcers of the skin through which the embryos are discharged on contact with water. On the other hand, with *Onchocerca volvulus* and *O. caecutiens,* which produce subcutaneous nodules of the skin, ulceration does not occur. In the other important *Filaria* that infect man the microfilariae are found in the peripheral blood, but in *Onchocerca* they are found in the lymph.

For several years we have been especially engaged in the study of onchocerciasis in western and central Africa and in Guatemala. This condition is characterized by the presence of subcutaneous fibroid nodules or tumors varying in size from 2 to 3 millimeters up to 5 or 6 centimeters in diameter. The location of these nodules or tumors and their number vary greatly in different individuals and in different parts of the world. The adult parasites, both male and female, are found in the center of the nodules, where the female gives birth probably daily to an enormous number of microfilariae, which circulate not in the blood but in the lymph spaces and apparently show a tendency to seek the light. They are found especially in the upper portion of the corium of the skin and the tissues of the eye, particularly the conjunctiva, iris and cornea. The adult parasites are the inciting factor of the nodules or tumors which are formed about them. Enormous numbers of microfilariae circulate in the skin and tissues of the eye, giving rise to inflammatory changes in many individuals who possess a special susceptibility to the products of metabolism and to the movements, death and disintegration of the parasites. Thus in the skin isolated or confluent pruriginous areas may occur. In other cases of long standing with severe infection with microfilariae, a xerodermatous condition of the skin may be produced. It is in the cases of long standing with tumors about the head and shoulders that disturbances of vision most frequently occur. In the eye the lesions consist particularly of a pericorneal conjunctivitis, iritis and keratitis, which not infrequently lead to loss of sight. Punctate keratitis is a common lesion. In the advanced cases vascularization of the cornea and proliferation of fibroblasts may occur. Infiltration and destruction of Bowman's membrane, and even of Descemet's membrane, sometimes occur, and pannus may be present. In advanced cases retinochoroiditis and optic atrophy may take place. In some cases degeneration of the papilla and early sclerosis of the choroidal vessels may be observed with the ophthalmoscope.

Lantern slides were shown illustrating the various pathologic lesions in the skin and eyes, as well as the location and character of the nodules. The methods of transmission and the intermediate hosts were also illustrated and discussed.

Sept. 1936

Superfamily FILARIOIDEA
Weinland, 1858; Stiles, 1907

I. Family FILARIIDAE (Cobbold, 1864) Claus, 1885

Subfamilies

1. SETARIINAE

Genus *Setaria* Viborg, 1795
S. hornbyi
S. poultoni
S. labiato-papillosa

Genus *Dipetalonema* Diesing, 1861.
Syn., *Acanthocheilonema* Cobbold, 1870
*A. perstans**
*A. ozzardi (Filaria ozzardi)**

2. DIPLOTRIAENINAE

3. CRASSICAUDINAE

*Pathogenic for man.

4. MICROPLEURINAE

5. LOAINAE
   Genus *Loa* Stiles, 1905
   *L. loa (Filaria loa)**

6. ONCHOCERCINAE
   Genus *Onchocerca* Diesing, 1841
   *O. volvulus**
   *O. caecutiens**
   O. gibsoni
   O. reticulata

7. FILARIINAE
   Genus *Wuchereria* Silva Araujo, 1877; Seurat, 1921
   *W. bancrofti (Filaria bancrofti)**
   Microfilaria malayi (?)*
   Genus *Dirofilaria* Railliet and Henry, 1911
   D. immitis
   D. magalhãesi

8. APROCTINAE

II. Family DRACUNCULIDAE Leiper, 1912
Subfamily
1. DRACUNCULINAE (Stiles, 1907)
   Genus *Dracunculus* Reichard, 1759
   *D. medinensis**
   D. globocephalus
   Genus *Philometra* Costa, 1845
   P. globiceps
   P. sanguinea

*Pathogenic for man.

TRICHINOSIS—INCIDENCE AND DIAGNOSTIC TESTS

BY DONALD L. AUGUSTINE, SC.D.*

DESPITE the fact that calcified cysts of trichinae were noted in dissecting rooms of Europe over a century ago and that trichinosis has been studied as a human disease for more than 80 years and is known to have been the cause of serious epidemics throughout Europe and North America, data regarding the incidence of this infection are astonishingly meagre and of but little value.

Trichinosis is practically unknown as an indigenous infection in the tropics. It is a characteristic helminth infection of the Northern Hemisphere and, as a human disease, is most prevalent in those countries whose inhabitants customarily eat raw or rare pork. It has been explained that the absence of this parasite in tropical countries is due to the habit of thoroughly cooking pork. Yet, if all pork in the tropics were thoroughly cooked, we should find infection with *Taenia solium*, the pork tapeworm of man, to be equally rare.

Statistics on the prevalence of trichinosis are, in the main, entirely misleading. This is particularly true of data published prior to 1931. Figures based upon case reports are inadequate, and those based upon autopsy findings are now known to be of little value. A figure quoted repeatedly in the past is that in about 2,000 necropsies approximately 2 per cent were found to be trichinous. The inadequacy of this estimation has been shown more recently by Queen, who reported on 344 consecutive necropsies in Rochester, New York, in which artificial digestion of diaphragms revealed 17.5 per cent infected with *Trichinella spiralis*. In another series of 59 diaphragms from necropsies in Boston, 27.6 per cent were positive. Recently, Riley and Scheifley examined the diaphragms of 117 cadavers in the anatomic laboratories of the University of Minnesota. Approximately 18 per cent were found to be trichinous. In a second series of 50 cases, 20 per cent were positive. Thus, in three large cities, widely separated in this country, the incidence of trichinosis appears to be about ten times greater than earlier estimations indicated.

During the past 4 years, we have made clinical observations on 75 patients with trichinosis. From this and similar studies of sporadic cases, it is evident that many patients ill with trichinosis are incorrectly diagnosed. This difficulty in diagnosis is due mainly to the bizarre and atypical clinical manifestations so characteristic of this disease. It is generally stated that the sporadic case and milder forms of the disease are particularly confusing and are often passed unrecognized by the attending physician. On the other hand, serious and even fatal cases not infrequently escape diagnosis. This was well illustrated during the 1924-1925 outbreak of typhoid caused by eating raw, contaminated oysters. In tracing the source of all reported typhoid cases, some 20 cases of active trichinosis were discovered here in Boston which had been diagnosed and reported as typhoid fever. Similar instances have been noted in Chicago and, undoubtedly, have occurred many times elsewhere.

Like many other infectious diseases, the diagnosis of trichinosis is relatively easy when it occurs in epidemic form and when suspected. There is scarcely a book of parasitology, general medicine or laboratory diagnostic methods that does not recommend an examination of the patient's blood, spinal fluid, feces or biopsy of muscle for direct evidence of the parasite. These attempts to demonstrate the parasite are so frequently unsuccessful that we believe them to be of doubtful value as aids in diagnosis.

Herrick and Janeway (1909) were the first to demonstrate the larvae in the circulating blood of man. The bloods of 3 patients of a family of 8 ill with trichinosis were examined

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for larvae. After more than an hour's search, 4 larvae were found in the blood of one. The success of this method has not increased with the years. All of our many attempts to find the larvae in the blood of human beings with trichinosis have been unsuccessful, and only occasionally have they been demonstrated in the blood of experimentally infected animals.

Trichinella larvae were first observed in the spinal fluid by Van Cott and Lintz in 1914. Others have since demonstrated them in spinal fluid. However, the diagnosis is usually correctly made before the parasites may be found in the spinal fluid and, since it is such an infrequent finding, one is not warranted in recommending a lumbar puncture as a routine clinical procedure in the diagnosis of trichinosis.

It is generally advised to examine the feces during the stage of diarrhea for adult worms. This method may have had its origin in the ease with which adult worms are usually found in the intestinal contents at autopsy. We have examined the feces of trichinous guinea pigs, rabbits, swine and men on innumerable occasions and not once were adult trichinellae detected in the stool. It is our opinion that searching for evidence of trichinella in the blood, spinal fluid and feces as a laboratory means of making the diagnosis is usually a waste of time.

A usual procedure employed in diagnosing trichinosis is the microscopic examination of excised skeletal muscle for larvae. In view of the high incidence of the disease in this country, the finding of larvae surrounded by thick connective tissue capsules or calcified capsules showing no inflammation is evidence that such are old larvae and unrelated to an acute condition. Sections of muscle obtained during the acute stage of the illness reveal larvae with surrounding inflammation and muscle destruction.

A biopsy must be considered a very unreliable means of making a positive diagnosis. From our own experience and a review of the literature, it appears that trichinella larvae are found in less than half of the biopsies. In most instances, the diagnosis has been made on the presence of myositis rather than on the presence of the parasite itself. Diagnosis by muscle biopsies is exceedingly uncertain. We have examined microscopically more than 80 bits of muscle from an experimentally infected pig without finding the parasite. Only after grinding up important skeletal muscles of this animal and digesting them in artificial gastric solution were trichinae found. We look upon the biopsy as an unnecessary procedure in the diagnosis, not only because of the uncertainty of finding parasites and the inconvenience to the patient, but because we now have other more reliable means of establishing the diagnosis.

Serologic and skin tests have been employed only recently in the diagnosis of helminth infections. Among the better known of these is the Casoni test—a skin reaction used extensively in the diagnosis of echinococcosis, which is generally recognized to be of great practical value.

In 1928, Bachman introduced a method for preparing trichinella antigen which could be used for skin and precipitin tests in the diagnosis of trichinosis. He detected precipitins in rabbit's serum about 30 days following infection with *Trichinella spiralis*, and also demonstrated a clearly delayed type of skin reaction in laboratory animals after less than a week's infection. Augustine and Theiler in 1932 confirmed Bachman's findings in laboratory animals and extended their observations to the investigation of the precipitin and skin tests in human and porcine subjects.

In preparing the antigen, guinea pigs are used exclusively. The muscles from an animal which has been infected with Trichinella 4 or 5 weeks previously are passed through a food grinder and then digested in a solution of pepsin and hydrochloric acid. The trichinae settle out in the container and are then washed repeatedly with water until they are free from host tissue. These larvae are dried, placed in ether for 24 hours, and then dried in a vacuum. They are ground in an agate mortar. To this, 100 parts of Coca's solution (NaCl, $NaHCO_3$ and phenol) are added. After 3 or 4 days, the whole mixture is filtered through a Seitz filter and sterilely transferred to small vaccine bottles. For the precipitin tests, the antigen is used in this 1:100 dilution. Higher dilutions are necessary for skin tests.

The precipitin test is done by overlaying 0.3 cc. of clear serum in a small tube with an equal amount of a 1:100 dilution of the trichinella antigen. A control tube contains 0.3 cc. of serum overlaid with Coca's solution. The tubes are placed in the water bath for 1 hour at 37.5°C. A positive test shows a white ring at the junction of the serum and antigen. The test is usually not positive until after the fourth week of the infection, but precipitins may be demonstrated as early as the second week. No change in the appearance of the reaction has been noted in trichinous patients 1 year after the infection. No positive "rings" were obtained with the serum from patients 5 to 7 years after infection, but positive flocculation tests were obtained at the end of 24 hours. In a few instances, the control tube may show a ring as well as the tube with the patient's serum and antigen.

In order to determine the specificity of the precipitin reaction, the tests were made in the interior of Colombia, South America, where trichinosis is unknown among the native popu-

lation. It was found that the administration of drugs, such as quinine and arsenicals, may cause "false positive" reactions, but under normal conditions positive reactions do not occur. In Boston, we have found the precipitin test positive in every case of trichinosis if performed during or after the fourth week of the disease.

In summary, then, the precipitin reaction in trichinosis usually becomes positive about the fourth week of the disease. It is especially useful if the test is at first negative and then, later in the disease, is found positive. In a few instances, a ring is found in both tubes and, rarely, false positive reactions may be observed after the administration of certain drugs.

The intradermal skin test is done by injecting 0.1 cc. of a 1:10,000 dilution of the trichinella antigen into one arm, and a similar amount of Coca's solution into the other arm. Immediately following the injections there is an erythematous flare, which quickly subsides. Within 5 minutes after the injection of positive reactors, a blanched wheal appears, sometimes with pseudopodia running out from it, with a pronounced area of erythema surrounding the wheal. The reaction reaches its maximum in 1 hour, and then gradually subsides. This is the immediate type of reaction which has been accepted by us and others as diagnostic for trichinosis. The skin test does not usually become positive until the second week of the disease, and may be elicited months and years after the acute illness has subsided.

Considerable confusion still exists in the intradermal use of trichinella antigen as a diagnostic test because various workers have interpreted their results after using different animal species. It is well recognized that the tissue response to foreign protein varies with the species used for study. Thus, Bachman stated that the reaction was a delayed type, basing his statement on tests done on rabbits and guinea pigs. However, Augustine and Theiler found that, while this was true for these laboratory animals, in human beings and swine the reaction was of the immediate type.

Another confusing factor resided in the dilution of antigen used for the skin test. Further studies on the natives of Colombia showed that a significant number gave positive skin tests with the 1:100 dilution of antigen, but negative precipitin tests. That these skin reactions were nonspecific was evident when higher dilutions gave negative tests. No reactions were obtained using a 1:10,000 dilution of the antigen. Later studies in Boston have found this dilution effective in producing typical, positive reactions in trichinous persons and in swine.

Up to within the last year, we believed that the skin reaction following the intradermal injection of antigen was always of the immediate type. However, we have recently had the opportunity of doing skin tests on patients ill only a few days with trichinosis. Skin tests performed on the second to the fourth day of the illness resulted in no immediate reaction, but 24 hours later there was a delayed, tuberculin-like type of reaction. This reaction has been elicited only during the first week of the illness; after that the response is of the immediate type. Precipitins have never been demonstrated at the time when the skin reaction is of the delayed type.

These two types of skin response in a patient hypersensitive to the protein of trichinellae are of considerable immunologic importance. Little is known concerning the mechanism of their production. Other workers in Boston have become interested in this phenomenon of two types of skin reactions in hypersensitive people. Mote and Jones, at the House of the Good Samaritan, sensitized rheumatic fever patients with rabbit protein. They, too, found that the first manifestation of a hypersensitive state was the delayed, tuberculin-like type of reaction, followed by the immediate type. Similar results have been reported by Simon and Rackemann, at the Massachusetts General Hospital, who sensitized individuals to guinea-pig serum. At the same hospital, Dienes observed a similar course of events in guinea pigs sensitized to egg white and horse serum.

In the application of any antigen for diagnostic skin tests, it is desirable to know how specific it is for any given disease. Our experience has shown that in a total of 60 cases of trichinosis, 59 gave positive skin tests with a 1:10,000 dilution of trichinella antigen. The 1 negative reaction occurred in a patient who entered the hospital in a moribund condition from trichinosis. We have encountered a number of individuals who had positive skin tests without further evidence of having acute trichinosis at the time. These so-called nonspecific reactions may be explained in different ways. If, as it has been shown by postmortem examinations, many individuals have had an unrecognized infection in the past, they will still have a positive reaction to trichinella antigen without any signs of the disease. Then, too, there is a group of individuals who show a marked skin sensitivity to the intradermal injection of any foreign protein. This is especially true of allergic individuals who suffer from hay fever and asthma. We have obtained the same type of skin reaction in an allergic person using trichinella antigen, sterile milk and horse serum. Recently, a young man entered the hospital with edema of the eyes and lips, fever and eosinophilia. Trichinosis was suspected and the skin test was positive; but he had a history of asthma and previous swelling of the face. No precipitins were found in his blood, and the obvious diagnosis was angioneurotic edema in an aller-

gic person. These nonspecific allergic reactions to trichinella antigen can be clarified if precipitin tests with the blood serum are done at the same time.

Another pertinent question concerning the specificity of trichinella antigen is the response of a nontrichinous individual harboring other parasites. McCoy and his colleagues at Rochester, New York, believe that nonspecific reactions may be due to the whipworm, *Trichuris trichiura*, which is closely related anatomically to *Trichinella spiralis*. However, this is contrary to our experience as well as that of Kaljus in Russia and Bachman in Puerto Rico. In relation to another parasitic disease, Kaljus observed that 2 patients with echinococcosis gave a clear-cut positive reaction with the echinococcus antigen and were negative to trichinella antigen injected at the same time. These observations appear to confirm the specificity of the two antigens.

Varying results with the skin and precipitin tests are to be expected from different workers. At the present time, no method has been elaborated for the standardization of trichinella preparations in terms of the antigenic fraction obtained from the material. Furthermore, there are instances where the antigen used was made from trichinella powder which contained an astonishingly large amount of undigested muscle tissue.

In the use of these tests, one must not lose sight of the fact that no biologic test is infallible. Any test employed should be considered in connection with other evidence. We have found the presence of an eosinophilia to be the most reliable laboratory aid in the diagnosis of trichinosis. Eosinophilia usually appears about the second week of the infection. Frequent examinations of stained blood smears are often necessary. Eosinophilia may be absent in the blood smears of severe and fatal cases, or in patients who have a complicating secondary infection.

In conclusion, it is again emphasized that trichinosis is not an uncommon disease in this country. The diagnosis of the sporadic case and the milder forms of the disease is always a tedious process and requires detailed study. The recognition and correct diagnosis depend on a careful history of the patient's illness, a complete physical examination, repeated examinations of blood smears for eosinophils, and the use of skin and precipitin tests.

THE STUDY OF THE PATHOGENIC RICKETTSIAE IN TISSUE CULTURE

Abstract

BY H. PINKERTON, M.D.,* AND G. M. HASS, M.D.*

THE etiologic agents of a large number of infectious diseases resist cultivation on artificial cell-free media. These agents may be divided into two main groups—the ultravisible, so-called filtrable viruses, and the microscopically visible, obligate intracellular parasites, of which the rickettsiae are excellent examples. The application of tissue culture methods to the study of both groups has given information of considerable value and has opened new routes of approach to important biologic problems. The rickettsiae are particularly favorable for morphologic study, because they can be clearly seen in the cytoplasm or nucleus of living or properly fixed and stained cells. These organisms are obviously "cytotropic" because they live only within cells, whereas in the case of the filtrable viruses we cannot be at all certain that this is the case.

The growth requirements of these cytotropic viruses and intracellular parasites are almost entirely unknown. For their life and multiplication, they depend in some way upon living cells, and nearly always upon specific types of living cells. This cell specificity suggests a specific interrelation between the metabolic activities of the parasite and those of its cell host. Presumably the parasites take advantage of certain metabolic or respiratory enzymes which their host cells contain but which they themselves lack. It was with the hope of finding a method of approach to this difficult and important problem that we have studied the rickettsiae extensively in tissue culture.

Temperature of incubation was found to be of primary importance in the intracellular multiplication of the rickettsiae. At 37.5° or at 41°C., infected tissues grow well, but become rickettsia-free and nonvirulent in a few days. At 32°C., rickettsiae multiply, grow massively in nearly all cells in the cultures, and remain indefinitely as a permanent addition to the cytoplasm or nucleoplasm of the cells. When cells are allowed to die, rickettsiae remain massed within their skeletons and never multiply in the surrounding clot. Changes in environmental conditions, such as pH, tonicity, O_2 and CO_2 tension, viscosity, anaerobiosis, inorganic salt concentration, and intentional contamination with free living bacteria, have not brought about extracellular multiplication or produced any appreciable effect on the intracellular mul-

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tiplication of the organisms, except when such changes have been lethal for the cells themselves. In this case, the rickettsiae survive the death of the cells for a few days only.

Correlation between the presence of rickettsiae in tissue cultures and the infectivity of such cultures was found to be complete. Since those cultures in which very few organisms were seen produced infections with prolonged incubation periods, this correlation may be said to have a quantitative as well as a qualitative value.

All strains of typhus which we have studied have shown typhus rickettsiae (*Rickettsia prowazeki*) massively distending the cytoplasm of cells in tissue culture without invading nuclei. All strains of spotted fever have shown massive intranuclear growth of the causative organism (*Dermacentroxenus rickettsi*) with relatively spare cytoplasmic involvement. (There are also important morphologic differences between the two organisms.) These distinctive cell infection patterns show no overlapping and are identical with the cell infection patterns of the microorganisms in their insect vectors. Attempts to alter these cell infection patterns by changes in the environment, including CO_2 and NH_3 tension, which are believed to alter intracellular pH, have been entirely unsuccessful.

These distinctive cell infection patterns seem, therefore, to be constant biologic properties of the two groups of organisms studied, and we have used them as an important criterion for the classification of strains of rickettsial disease which were clinically and even immunologically ambiguous (by immunologically ambiguous we mean that crossed immunity tests gave ambiguous results). On the basis of these studies we believe that all reported human rickettsial diseases, with the probable exception of the mite-borne diseases, in spite of wide, clinical variations, should be considered as caused only by strain variations of typhus (etiologic agent, *Rickettsia prowazeki*) and spotted fever (etiological agent, *Dermacentroxenus rickettsi*).

Although it seems best not to generalize at present, the observation of compact, spherical, intranuclear clusters of minute spotted fever rickettsiae in tissue cultures should, we think, be taken as evidence that certain of the so-called "inclusion bodies" (intracytoplasmic and intranuclear structures of unknown nature found in tissues infected with filtrable viruses) may be colonies of microorganisms too small to be seen as individuals. In this respect, the rickettsiae may be considered as forming a "missing link" between bacteria and certain of the viruses now classed as filtrable or ultravisible.

OXYGEN THERAPY

A Modification of the Box Method for Giving 95 Per Cent Oxygen

BY ALEX. M. BURGESS, M.D.*

THE use of 95 per cent oxygen in the treatment of gaseous distention of the intestines, as described by Fine, Banks, Sears and Hermanson,[1] creates a need for a simple, reliable and inexpensive method for its application. Furthermore, in many conditions of anoxemia in which there is obstructed dyspnea it may be advisable to raise the oxygen content of the inspired air to a very high concentration for a few hours. In the present communication an apparatus is described, which, it is believed, will fill this need.

The methods now in use for giving high percentages of oxygen are open to various objections. In emergencies the mask may be employed, but for short periods only. The nasal inhaler, as used by Evans and Durshordwe[2] probably does not deliver pure oxygen continuously over a long period, as leakage caused by the movements of the patient and mouth breathing apparently cannot be avoided. Neither by nasal catheter, open box nor tents of the types in general use can a concentration of over 80 per cent be reliably maintained. The oxygen room is ordinarily precluded on account of the great expense involved.

Fine and his associates[1] have described an apparatus that appears to be efficient, but it is expensive and cumbersome and involves the use of a motor. In applying this method it has been found most convenient to keep the patient in a sitting position, which would seem difficult for patients who are very ill and suffering from severe distention.

The apparatus here described is a simple adaptation of the open box or "tent".[3] The modification consists of closing the box by a rubber cover, which is made snug around the frame by rolling its edge with that of the removable hood that is used in the commercial open boxes that are now in general use. An opening in this cover is made to fit tightly about the opening of the cooler so that ice may be introduced from time to time without uncovering the apparatus. This gives a tightly closed space in which the patient's head lies, as described in the use of the open box method.[3] The modern type of rubber hood is made to fit snugly yet comfortably around the neck and is easily adjustable. Removal of carbon dioxide is accomplished by soda-lime, which is contained in a tray attached to the cover of the cooler.

If this apparatus were tight it would be nec-

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essary to allow for the escape of gases by using a flutter valve, such as is illustrated in fig. 1. It was found, however, that there is sufficient leakage about the neck and elsewhere so that such a precaution is unnecessary. It is evident

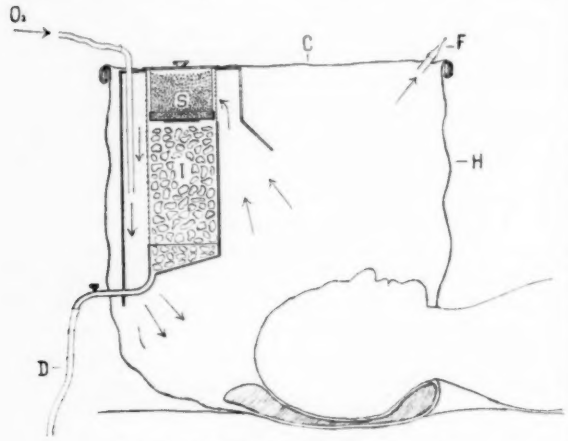

FIG. 1. Diagram of apparatus in use.
H—Hood
C—Cover
F—Flutter valve
S—Soda-lime
I—Ice
D—Drain tube

that the tighter the whole apparatus can be kept the lower the oxygen flow that will be needed to keep the concentration within the apparatus at 95 to 98 per cent. For this reason it is probably better not to use a flutter valve. Figure 2 shows the apparatus in use on a patient.

FIG. 2. Apparatus in use. The attendant is adding ice. The cover of the cooler is held in his hand and shows the tray of soda-lime.

In testing this apparatus it was found that in about 40 minutes the nitrogen was washed out and a concentration of 95 per cent oxygen obtained. This rose to 98 per cent and remained at that point throughout the test, even though the rate of flow was reduced to 3 liters per minute. This is graphically illustrated by figure 3. Samples for testing were obtained by means of a rubber tube introduced through a small hole in the cover of the apparatus and allowed to hang down over the patient's face. A check test, using pure oxygen drawn from the cylinder, showed that with the method used 98 per cent was the highest reading that could be obtained.

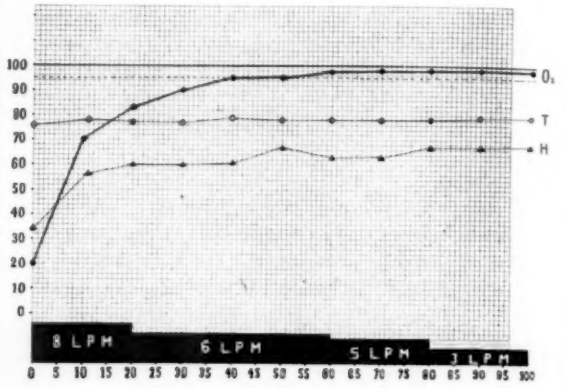

FIG. 3. Chart showing the oxygen concentration during a test lasting 1 hour and 40 minutes. The temperature and humidity are also shown, and the oxygen flow in liters per minute. Time is in minutes.

In the test illustrated by figure 3, the temperature and humidity values are not so good as might be expected, probably because finely chopped ice was used. Another test in which ice cubes were employed showed a maximum relative humidity of 64 per cent and a temperature of 69 to 70°F. in a room in which the relative humidity was 40 per cent and the temperature 70°F. Repeated tests for carbon dioxide failed to show more than traces. The patient showed no increase in respiratory rate and experienced no discomfort.

It is probable that this apparatus can be used for the application of oxygen-helium mixtures, as described by Barach,[4] if care is taken to prevent leaks. If, for example, the rubber hood and cover were made in one piece and fitted about the opening for the cover of the cooler, the practical elimination of all leaks except about the patient's neck would be accomplished.

SUMMARY

A simple and inexpensive apparatus for the administration of oxygen is described.

Tests of this apparatus show that by its use an oxygen concentration of 95 to 98 per cent can be maintained for as long as it is needed.

It seems probable that the apparatus can be used for the administration of oxygen-helium mixtures.

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TRAUMATIC INTRAPERITONEAL RUPTURE OF THE BLADDER*

Report of a Case

BY F. J. C. SMITH, M.D.†

INTRODUCTION

TRAUMATIC rupture of the bladder is one of the few acute emergencies encountered in urology, according to Hinman.[1] The condition is relatively rarely encountered yet merits attention because of the increasing importance of automobile accidents as an etiologic factor.

This particular case had certain interesting aspects peculiar to it. The surgical treatment differed from that most commonly used. There was a concomitant injury to branches of the sacral plexus resulting in neurological changes.

REPORT OF CASE

A 28 year old man was driving his automobile home, when it overturned, pinned him beneath it and rested across his lower abdomen and pelvis. A companion was unable to extricate the victim and walked up the road for assistance. The time during which the patient was submitted to the pressure of the car was estimated as 15 to 20 minutes. He was then removed and taken to the hospital. He did not remember exactly how long before the accident he had last voided, although it had been at least 2 hours, and he had consumed a couple of pints of beer in the interim.

The past history was irrelevant.

Physical examination on admission to the accident room showed a well-developed and nourished man with a white face and cold extremities. There were beads of perspiration on a cool forehead. The temperature was 99° F., the pulse 90, and the blood pressure 110 systolic, 60 diastolic. The patient was conscious, quiet and cooperative. He complained of moderate pain in the lower abdomen and over the right hip laterally and posteriorly to the head of the femur, where there were several linear pressure indentations, 2 to 3 mm. in depth, in the skin overlying the course of the sciatic nerve on both sides of the sacrum and pelvis.

Abdomen: There was no distention. The abdomen was soft and without any signs of tenderness throughout both upper quadrants. There was a slight resistance in both lower quadrants but no true spasm. Diffuse tenderness was present in the lower abdomen, especially in the left lower quadrant and suprapubically. However, the tenderness was not extreme. Percussion suggested a diminution of the normal tympany over the entire abdomen and more in the flanks. No attempt was made to determine shifting dulness. Peristalsis was absent throughout on auscultation. The quadriceps and posterior tibial reflexes were absent in the right leg. The quadriceps reflex was present in the left, but the posterior tibial was absent. No response was elicited to plantar stimulation, although no definite anesthesia was recognized. There was no clonus. The head, eyes, ears, nose, throat, heart, lungs and upper extremities were negative. Passive motions of both legs were not limited. There was no evidence of fracture. Active motion was limited and on the right caused pain in the gluteal region. An x-ray taken of the pelvis, lumbosacral spine, and upper femora showed no evidence of fracture.

The patient received emergency shock treatment and was given morphia with rapid improvement in the color and warmth of the skin and extremities. He was placed on the danger list. The diagnosis made on his admission questioned internal injury. During the next 6 hours sufficient changes appeared to make a definite diagnosis of an internal injury. The patient vomited on two occasions. The pain in the lower abdomen became more acute and there were more tenderness and spasm. The upper abdomen was still unremarkable. No peristalsis was heard. The temperature rose to 100.2°F. by mouth and the pulse to 120. The white blood cells were 16,000 per cmm. The differential white count showed 52 per cent adult polymorphonuclear leukocytes and 31 per cent band forms. The blood pressure rose to 140 systolic, 80 diastolic.

Rectal examination gave the most conclusive information, consisting of a fullness in the dependent portion of the peritoneum above the prostate, with exquisite tenderness. Catheterization yielded about 20 to 30 ounces of urine of normal gross appearance. Examination by microscope showed 8 to 20 white blood cells per high power field and 10 to 25 red blood cells. The specific gravity was 1.010. There was a heavy trace of albumin, a neutral reaction and no sugar.

An exploratory laparotomy with suture of traumatic intraperitoneal rupture of the bladder was performed under gas-oxygen-ether anesthesia. A left paramedian incision was made extending from the umbilicus to the symphysis pubis. When the peritoneum was opened considerable straw-colored fluid, similar in appearance to urine, escaped. A hand was inserted suprapubically, and the fingers encountered a 4 to 5 cm. rent in the posterior superior surface of the bladder through which the inlying catheter could be felt. The abdominal cavity and pelvis were emptied of urine by suction. Several soft strings of coagulated fibrin were removed from the depths of the pelvis. No odor suggestive of the colon bacillus was present. The intestines, liver, kidneys and spleen were normal to palpation, and there was no gross blood present. The bladder was sutured in four layers without drainage: namely, mucosa, muscularis, serosa and peritoneum. A continuous chromic no. 1 catgut was used for each. The abdominal wall was closed in layers without drainage. The decision to close both bladder and abdomen tightly was made because the patient was young, healthy and had no evidence either of stagnated urine or of infected bladder. The relatively slight febrile reaction with slow onset, as well as the appearance of the intestines, was further evidence that the peritonitis was relatively aseptic. Past experience with perforated duodenal ulcers has showed that the peritoneum will control much infection as long as surgical intervention is early and the gross soiling evacuated, followed by closure of the perforation. It was believed, therefore, that the peritoneum would likewise resist any latent infection in this instance, as the nature and virulence of the bacterial flora in the urine could hardly be more serious than in the intestinal tract. The bladder was placed on constant urethral drainage through a no. 22 French catheter. The intake and output were charted and watched carefully to see that the catheter never became plugged.

The patient was placed on Ochsner's regime postoperatively; namely, nothing by mouth, high Fowler's position, and morphia gr. 1/6 sc. by the clock

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every 3 hours. The fluid intake was maintained by the administration of 1,000 cc. of 5 per cent glucose in normal saline solution twice daily.

The postoperative course was uneventful except for a massive pulmonary collapse on the second postoperative day with an abrupt elevation of the temperature, pulse and respirations to 105°F., 140 and 30 respectively. This cleared within 48 hours after the patient's position was frequently changed. Ten grains of ammonium chloride and 5 grains of methenamine by mouth three times a day was ordered on the third postoperative day. Past experience in many cases of atelectasis postoperatively has yielded good results with 5 to 10 grains of ammonium chloride by mouth as often as every 3 or 4 hours. Cases have usually recovered within 24 to 48 hours.

The bladder was irrigated once daily with sterile boric acid solution, a one ounce asepto syringe being used. The catheter was removed on the twelfth day, and the patient was moved from his bed to a chair. He voided spontaneously 3 hours later. On the following day he voided 13 ounces at one time without discomfort. He was instructed to void at more frequent intervals in order to prevent overdistention of the bladder; however, he continued to void 10 to 15 ounces each time.

Four weeks after the operation the wound was well healed, and the patient was in a wheel chair on the ward. He remained incapacitated from peripheral nerve injuries.

Examination of the function of individual muscles at this time showed the following:

	Right	Left
Sartorius	Normal	Normal
Quadriceps femoris	Weak	Normal
Adductors	Normal	Normal
Gluteus Maximus	Normal	Absent
Medial Hamstring	Normal	Normal
Lateral Hamstring	Normal	Absent
Rotators of thigh	Normal	Normal
Tibialis anticus	Normal	Absent
Extensor hallucis longus	Normal	Absent
Extensor digitorum longus	Normal	Absent
Peroneals	Normal	Absent
Posterior crurals		
Superficial	Normal	Absent
Deep	Normal	Absent
Muscles of the foot	Normal	Absent

Lumbar puncture yielded a grossly normal spinal fluid. The dynamics were normal and gave no indication of block such as may result from a ruptured intervertebral disk. The albumin, globulin and cell counts were normal. There was no xanthochromia. These findings were confirmatory evidence of peripheral nerve injury. The patient was discharged from the hospital on crutches 6 weeks after the accident. The left lower leg was in a plaster shell to counteract foot drop.

He was re-examined 2 weeks after discharge at which time the muscles of the left leg and foot showed some return of function. Eight weeks after the injury he was able to walk unsteadily without crutches, as the muscle groups were rapidly recovering from paralysis. He was referred to Dr. Charles S. Kubik, neurologist on the staff of the Massachusetts General Hospital, for consultation. The following is from the report on his examination:

"The findings indicate a bilateral and somewhat scattered or patchy disturbance affecting not only muscles supplied by the sciatic nerves but quadriceps as well. I should suppose that one of two possible causes may have been responsible, pressure on large vessels or direct pressure on nerve trunks. Because of the patchy distribution I should favor the latter view. In any case it is perfectly clear, I think, that the present conservative, expectant treatment should be continued and, judging by the improvement which has already taken place, I should look for a fair degree of recovery."

SUMMARY

1. A case of traumatic intraperitoneal rupture of the bladder is reported in which the surgical treatment varied from that commonly used in that the bladder and abdominal wall were closed tightly without suprapubic drainage.

2. Automobile accidents are of increasing importance as an etiologic factor in this injury.[2]

3. The patient probably had a distended bladder at the time of the accident, as is the usual history.

4. The rent in the bladder was in the location usually described for this injury.[2]

5. Concomitant injury to branches of the sacral plexus resulted from pressure ischemia in the nerve trunks and caused complete paralysis of multiple groups of muscles for several weeks.

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NEW HAMPSHIRE MEDICAL SOCIETY

RECENT DEATHS

OLIVER—Robert Freeman Oliver, M.D., of Bradford, New Hampshire, died at his home, February 5, 1937. He was in his seventy-fifth year.

A native of Charlestown, Dr. Oliver was graduated from the University of Vermont College of Medicine in 1890. Before going to Bradford, where he had practiced medicine for the past fifteen years, he had also practiced at Stockbridge, and at Alstead, Enfield and Warner, New Hampshire.

He was a member of the New Hampshire Medical Society and the American Medical Association, of the courtesy staff of the Margaret Pillsbury Hospital at Concord and the staff of the Carrie Wright Hospital at Newport.

Mrs. Gabraella O. Oliver, his widow, and Raymond H. Oliver, a son, survive him.

WHITE—William H. White, M.D., died at his home in Goffstown, N. H., on February 17, 1937, after a short illness. He was 62 years of age.

Dr. White was a graduate of the Detroit College of Medicine and Surgery, receiving his medical degree in 1901. He practiced in Vermont until 1917 and was a member of the Medical Service Corps during the World War. For twelve years thereafter he was with the South American Gold and Platinum Company at Andagoya, Colombia. In 1930 he attended the School of Public Health at Harvard University.

During the last 3 years Dr. White had been in private practice at Goffstown, N. H., where he was on the staff of the Hillsborough County Hospital.

Dr. White was a member of the Manchester Medical Association, the New Hampshire Medical Society and the American Medical Association.

He is survived by his widow.

CASE RECORDS
of the
MASSACHUSETTS GENERAL HOSPITAL

ANTEMORTEM AND POSTMORTEM RECORDS AS USED IN WEEKLY CLINICOPATHOLOGICAL EXERCISES

FOUNDED BY RICHARD C. CABOT, M.D.

TRACY B. MALLORY, M.D., *Editor*

CASE 23111

PRESENTATION OF CASE

A 42 year old American businessman was admitted complaining of attacks of pain in the left lower quadrant.

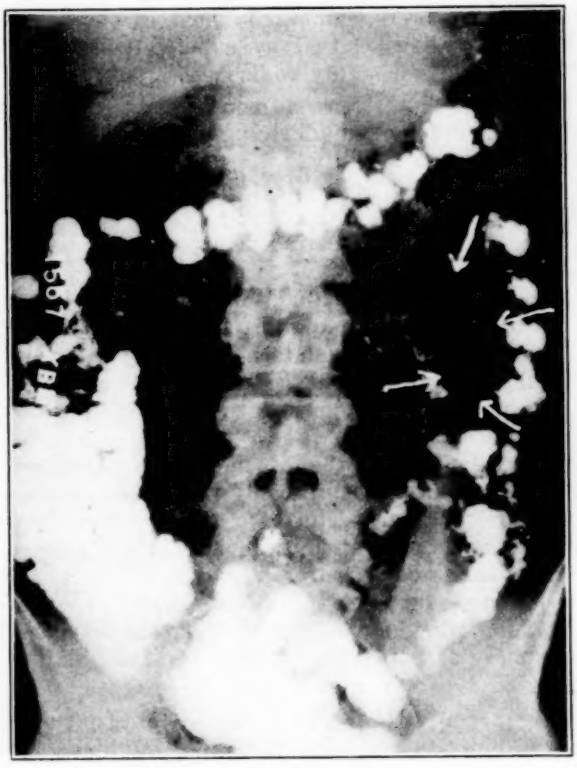
Four months before entry the patient was seized with a severe attack of pain in the left lower quadrant. The pain was rather dull and not colicky in character. On one occasion he had nausea and vomiting, but there was no diarrhea or change in bowel habit. Associated with the attack, which lasted for 2 or 3 days, was considerable lassitude. The pain subsided without treatment. A month later he had another similar attack, and since that time the dull pain in the left lower quadrant, although less in degree, has been present constantly. A physician was consulted, and a Widal test was done. This was said to be positive and the patient was then isolated for 6 weeks. He was released from quarantine after 3 negative stool cultures. No note was made as to whether a positive culture had ever been obtained. Following his discharge an x-ray demonstrated a tumor in the abdomen, and he entered this hospital.

Physical examination showed a well-developed and nourished man in no acute discomfort. The heart was negative. The lungs were clear. The blood pressure was 120/80. A large firm mass was palpable in the left flank, extending from beneath the costal margin to a point near the crest of the ilium. This mass was tender on deep palpation and did not move with respiration. Rectal examination showed a lemon-sized mass on the floor of the pelvis that presented a hard, fixed, distinct border to palpation.

The temperature, pulse and respirations were normal.

Examinations of the urine were negative. Stool examinations gave 1+ reactions to the guaiac test. The blood showed a red cell count of 5,600,000, with a hemoglobin of 85 per cent. The white cell count was 14,500. The differential smear showed 79 per cent polymorphonuclears; 7, lymphocytes; 9, monocytes; 3, eosinophils and 2, basophils. The sedimentation rate was 28 millimeters in 1 hour. A blood Hinton test was negative.

A barium enema filled the colon readily. There was no evidence of intrinsic disease. The palpable mass in the left lower quadrant lay in front of the descending colon and could not be separated from it. The descending colon moved with the mass but there was no evidence of invasion of the colon. There was an oval air-filled cavity in the center of the palpable mass, and at its lower end the cavity showed haustra-



The air-filled, barium-coated cavity marked by arrows represents the lesion. Examination 4 hours after motor meal. (AOH)

tions of normal bowel. At 1 hour intervals after the patient had ingested barium the esophagus, stomach, duodenum and upper jejunum were essentially normal in appearance. After about 4 hours the barium was about to enter the region of the mass, and at 6 hours it had passed the mass and was almost entirely within the terminal ileum. There was, however, some barium within the gas-containing area in the mass, and it appeared to coat the inside of an irregular cavity. There was no evidence of obstruction in the small bowel; in fact there was probably hypermotility in the region of the mass. The spleen appeared to be at the upper limit of normal size. The liver was not definitely enlarged. The kidney outlines were normal, and the lung fields were clear.

For 4 days following entry the patient's temperature fluctuated between 98° and 99.8°F. On the fourth hospital day a laparotomy was performed.

Differential Diagnosis

Dr. Richard H. Miller: A severe attack of pain coming on suddenly, as I assume this did, suggests something serious of an organic nature, and one immediately thinks of a perforation. Then the fact that the pain was not colicky, but dull and constant, suggests an inflammatory process, perhaps local peritonitis, rather than an obstructive lesion. The pain subsided so that, whatever happened, the process must have been temporarily held in check. It may have been caused by a small perforation which was thoroughly walled off.

The similar attack a month later, however, suggests that some underlying pathologic process was going on steadily.

This story of possible typhoid fever strikes me as perhaps a red herring drawn across the trail. If I were treating this patient, I would check very carefully to see if he really did have typhoid. If he had a Widal test the doctor would not have done it in his own office, but it must have been sent to a laboratory, and one would think it would be possible to check it. My inclination is to believe that he did not have the disease.

Had the mass in the left flank been the spleen or the left kidney it probably would have moved with respiration. The fact that it was fixed fits in with my previous thought that it is of an inflammatory nature.

If one can take the rectal examination at its full value one will be obliged to interpret the mass as a pelvic metastasis or transplantation of a cancer higher up. It is our custom in all cases where we suspect cancer of the stomach to do a rectal examination and if we feel a rectal "shelf," which it strikes me is being described here, we immediately conclude that the cancer is very extensive, has migrated into the pelvis and has begun to grow there. So from this point on I assume that, whatever is going on, there is some intra-abdominal malignancy.

There is a small amount of blood, as evidenced by the one plus reaction to the guaiac test, which would again fit in with my previous assumption.

The blood examination I interpret as being no different from what one might find in a more or less chronic inflammatory process.

The x-ray examination is extremely interesting and unusual. I would expect that there was no cancer in the colon. "The descending colon moved with the mass but there was no evidence of invasion of the colon." Therefore, whatever this was, so far as we have gone we must think of an underlying malignancy with infection superimposed on it, producing a tumor mass which pushed the descending colon backward.

"There was an oval air-filled cavity in the center of the palpable mass and at its lower end the cavity showed haustrations of normal bowel." That to me means that something has caused a local perforation of the bowel and therefore has developed a cavity into which the air contained in the bowel has been able to enter.

Consonant with what I have already mentioned, the spleen seems to be within normal limits and the liver not definitely enlarged.

I have already said that I would make a diagnosis of some original cancer. Diverticulitis might conceivably account for this perforation in an atypical way, but an inflammatory mass would not, in my opinion, give rise to what is described in the pelvis, that is, a hard mass with a "shelf". The same applies to regional ileitis, which sometimes occurs, not in the terminal ileum, but higher. That again, I believe, would not account for this pelvic mass. Some type of lymphoblastoma would have to be considered, but I would be inclined to rule it out because I do not think it usually occurs in this manner. Typhoid again comes to mind, and one might possibly consider that the patient had a mild "walking typhoid" infection and a localized perforation, but again I think that has nothing to do with the final picture, because whatever happened it would be purely inflammatory and again would not account for the pelvic mass. The appendix I have thought about and ruled out. It happens that I have been extremely interested in Meckel's diverticulum, and I know that very extraordinary things happen in this condition. In a large proportion of the cases there is gastric mucosa which secretes acid and gives rise to a neighboring peptic ulcer, a peptic ulcer that may bleed or perforate; and, also, there are cases recorded of malignant disease in Meckel's diverticulum. A cancer developing in a diverticulum might possibly account for such a condition. A cancer would grow and perforate and then there would be a local area of infection followed by a large surrounding inflammatory mass, but a cancer of Meckel's diverticulum is so extraordinarily uncommon that, although I would put it down as number two, I would not actually make that diagnosis. A cancer of the small intestine could account, in my opinion, for everything that is here described. I have seen one case not unlike this in which a malignant polyp of the lining of the small intestine became adherent to the pelvic structures and there was a partial perforation. I operated on the patient and separated the small intestine from the uterus, finding an open hole in the ileum.

I will conclude by making a diagnosis of cancer of the lower small intestine which has perforated, forming a local cavity containing pus, and a very large surrounding inflammatory mass, characterized by having loops of small intestine stuck to it.

X-ray Interpretation

Dr. Aubrey O. Hampton: This is a plain film of the urinary tract showing the gas-containing area that was so interesting. It is elongated and is somewhat the shape of the large bowel, but shows small bowel haustrations only at the lower end. This is a barium enema, and you can see that the descending colon is perfectly intact. Here is the area of the palpable mass. Still we have this air-containing cavity of almost exactly the same shape and in the same location as before. The descending colon is pressed on and twisted. After evacuation there is no obstruction, but this air cavity is still present. Here is another film taken immediately after a drink of barium was given. In the upper part of the small bowel everything is normal, but in this film again you can see the air-filled cavity and the evidence of pressure on the colon. In this next film, 4 hours later, the barium has passed along into the jejunum and is just beginning to enter the area of the air. Here is a final film taken 1 or 2 hours later. All of the barium has passed through the suspicious area very hurriedly. What we were trying to do was to observe the patient at a time when this area was filled. Instead of examining him every 30 minutes, however, we examined only every hour, so we missed it. At one examination, however, we did see the cavity partially filled with barium, and the picture differs from that of a perforation considerably, I think, in that if this were a cavity external to the bowel into which barium flowed, the barium would not be distributed so evenly over the entire cavity. It would be in globules or in an irregular mass. So we assumed that the cavity was continuous with the lumen of the small bowel. Dr. Lingley[1] has looked up all the tumors of the small bowel and has found two definite types, obstructing and nonobstructing. This one fitted in with the nonobstructing, ulcerating type of tumor of the small bowel. The lumen of the bowel is characteristically enlarged instead of reduced, and in one of these cases, in fact, the small bowel containing the tumor was so large that it was thought by the surgeon to be the colon. We made the same diagnosis that you made, Dr. Miller, ulcerating malignancy of the small bowel, probably cancer.

Clinical Discussion

Dr. Arthur W. Allen: First of all you wonder why we operated upon a man with such extensive malignancy, and Dr. Hunter will talk of that phase of the subject a little later.

At operation we found a very extensive process involving primarily the small bowel at approximately the junction of the jejunum and the ileum. The growth had invaded the descending colon, so that the entire mass was one that would measure eight inches long by five inches wide. In addition we found many metastatic areas, mainly in the pelvis. Dr. Miller's deductions from the story as it is given here are absolutely correct. The only hitch is the type and character of the lesion. It was possible, after having a frozen section and thus knowing the character of the lesion, which, incidentally, had been suspected by Dr. Hunter, to justify ourselves in removing the primary focus of the growth. So we resected the involved portions of the small and large bowels and the patient made an uneventful recovery.

Dr. Francis T. Hunter: There is one point I might mention. This patient was running a temperature while in the hospital, and had probably had more outside when the diagnosis of typhoid was made. That is not a common thing for cancer of the bowel. However, as I recall it, I did not make the diagnosis.

Clinical Diagnosis

Tumor of the small bowel.

Dr. Richard H. Miller's Diagnoses

Carcinoma of the ileum with perforation and abscess cavity.

Metastasis in the pelvis.

Pathological Diagnosis

Lymphosarcoma of the ileum.

Pathological Discussion

Dr. Tracy B. Mallory: The specimen that was sent over after operation explains very clearly the x-ray picture. The small bowel that was resected was about 18 centimeters long, and in the middle of it was a tubular enlargement with tremendous thickening of the wall of the gut, and also very marked dilatation of the lumen. Here is the large bowel, a comparatively small structure adherent on this side. The tumor had invaded the outer layers of the wall of the colon and could not have been separated from it with safety, I believe.

Microscopic examination showed a very typical lymphosarcoma. This patient has a postoperative history which perhaps is worth continuing.

Dr. Hunter: After the patient was back to a normal diet and doing well, we began radiating the pelvis. The rectal tumor quickly disappeared. The man had another episode of mechanical difficulties, but that was adequately taken care of and, as far as I know, he is in good shape at the present time.

Without question this is the proper way to handle intestinal lymphoma because in our experience attempts to treat these tumors in the gut with radiation alone had been very unsuccessful.

DR. MALLORY: About 4 months after this operation the patient developed obstruction again and was operated upon a second time by Dr. Allen. On this occasion an inflammatory stricture in the immediate region of the first operation was found. There was no evidence of a local recurrence. He had in the interval developed a subcutaneous nodule and that was biopsied and also showed lymphosarcoma.

DR. ALLEN: At the second operation it was very interesting to see how absolutely free of tumor this abdomen was. There was no tumor anywhere within it. The x-ray had entirely melted all the intra-abdominal metastases. The constriction that had taken place in the descending colon where the suture had been done was due to the fact that there was a good deal of surrounding malignant tissue that had been radiated so heavily that he got a definite inflammatory reaction. Also, there was a loop of small bowel stuck in the pelvis where the chief metastases had been. This also had to be freed and resected.

DR. GEORGE W. HOLMES: I should like to comment on Dr. Allen's last remark. I think this is a good example of what we have been afraid would happen if we radiated over any part of the bowel heavily when it was infiltrated with lymphoma; there is a risk of getting an inflammatory reaction because of infection from the intestinal tract. Some of these areas involve the wall of the bowel in such a way that if destroyed by x-ray the contents of the bowel are allowed to seep. There is no inflammatory reaction from lymphoma unless there is infection, so far as I know. This case illustrates the danger of irradiating a hollow viscus.

A PHYSICIAN: How long can you keep the condition under control with radiation?

DR. HOLMES: If you generalize, I should say that the average duration is 3 years. If you pick out an individual, I have no idea.

DR. HAMPTON: Is it not true that in general the lymphomas of the bowel that have been operated upon have done better than the others? It is reported that patients with lymphoma of the lymph glands, treated only by x-ray, do not do so well as these people who have lymphoma of the bowel.[2]

DR. HOLMES: That is true, if it is the only lesion they have. Three or four cases with primary lesions in the gastrointestinal tract removed at operation have remained well for a long period of time, about 15 years.

DR. MALLORY: A certain number of cases of lymphosarcoma of the stomach are cured for 10 years with surgical resection without radiation.

DR. HUNTER: This man developed skin nodules so quickly that it makes me feel as if the outlook were not so cheerful as it might otherwise have been.

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CASE 23112

PRESENTATION OF CASE

A 53 year old Canadian laborer was admitted complaining of diarrhea.

About 5 weeks before entry the patient, who had been previously well, returned home after a hard day's work and had several loose bowel movements associated with griping pain in the lower abdomen. The diarrhea continued, occurring about three or four times daily. The stools consisted of a moderate amount of thin, slimy material. Previous to the onset of this illness his bowel movements had been rather retarded, occurring one to three times a week. The pain, which was located beneath the umbilicus, occurred about 10 to 30 minutes after meals, and was usually relieved by the passage of flatus. Associated with the intestinal symptoms were anorexia and weight loss, the amount of which was not known. There was no vomiting, but he was occasionally nauseated. Three weeks prior to admission the patient was suddenly seized with intense burning pain in the region of the anus, and examination at that time showed the presence of hemorrhoids. He had known of these varices for about 3 years but they had never caused him any inconvenience. The anal discomfort was so severe that the patient was compelled to go to bed. Occasionally following the passage of a stool he had a small amount of bleeding.

Physical examination showed a well-developed, undernourished, tired looking man, suffering from considerable pain in the anal region. The right pupil was larger than the left, but both reacted normally to light. Oral hygiene was poor but the tongue was normal in appearance. The heart was normal. The lungs were clear. The abdomen was scaphoid. Examination revealed no tenderness, spasm or palpable masses. Rectal examination showed a large pea-sized external hemorrhoid, which was quite red and tender. Introduction of the finger into the rectum caused severe pain and spasm, with the expulsion of considerable bloody material containing minute particles of feces. Palpation of the internal sphincter revealed many smooth, soft irregularities. The prostate was normal.

Proctoscopic examination caused a great deal of discomfort. The mucous membrane of the rectum was reddened but no ulceration or other abnormality was noted although the proctoscope passed for a distance of 15 centimeters. Higher examination was not possible because of the presence of feces. Within the anal canal were several large hemorrhoids, and on the anterior surface was a 2 centimeter friable ulcer which

appeared to be 1.5 centimeters in depth. This lay between the internal and external sphincters.

The temperature was 99.4°F., the pulse 72. The respirations were 18.

Examination of the urine showed a specific gravity of 1.030. The sediment contained an occasional white blood cell but was otherwise negative. The blood showed a red cell count of 4,400,000, with a hemoglobin of 70 per cent. The white cell count was 12,000, 85 per cent polymorphonuclears. Repeated stool examinations showed 3+ to 4+ reactions to the guaiac test. No amebae or other parasites were seen. A blood Hinton test was negative. The serum protein was 5.9 grams per cent. An intradermal injection of tuberculin in a dilution of 1:20,000 gave a negative reaction at the end of 48 hours.

X-ray examination of the chest was negative. A barium enema passed as far as the junction of the sigmoid and the descending colon, following which it was expelled. A second barium enema under considerable pressure could not be forced any farther than this point. The appearance was that of an obstructing lesion of the sigmoid, although the lesion itself could not be demonstrated. The liver appeared to be considerably enlarged in the films taken.

The day following entry the patient's temperature rose to 104°F. Subsequently it ranged irregularly between 98.6° and 102°F. His general condition remained unchanged and he continued to have tenesmus, diarrhea and occasional bloody stools. Cramps were relieved by paregoric, and his appetite was slightly improved. On the twenty-third hospital day another barium enema again passed only as far as the junction of the descending and sigmoid colon. After amyl nitrite, however, the barium passed slowly as far as the hepatic flexure although a portion of barium was expelled continuously throughout the examination. Study of the mucosal pattern after defecation showed it to be considerably thickened. There was no evidence of a mass at this time, and no definite evidence of obstruction. The red cell count had diminished to 2,700,000, with a hemoglobin of 65 per cent. Repeated stool examinations for amebae were negative. About 28 days after admission a gastrointestinal series showed that at the end of 6 hours the barium meal had passed well into the transverse colon. The cecum was barely outlined and appeared to be quite irritable and spastic, but showed no definite filling defect. An attempt to fill the cecum was unsuccessful. The patient's condition became progressively worse, diarrhea became severe and frequent, and the abdominal cramps returned. The abdomen became slightly distended, with a moderate degree of generalized tenderness. The patient developed hiccoughs and died on the thirty-second hospital day.

Differential Diagnosis

Dr. Edward L. Young: A patient in this age group coming in with a presenting symptom of diarrhea makes us think first of a local condition in the large bowel: carcinoma, colitis, possibly diverticulitis. At the same time we must not forget the possibility that achlorhydria associated with carcinoma of the stomach might be causing the diarrhea. It is unusual but does occur occasionally. If it is true that he was well up to 5 weeks before entry and that this whole process from health to death is actually only about 9 weeks, we are dealing with a process that is more acute than malignant disease ordinarily is. The history states, however, that bowel movements previous to the onset had been retarded, and since we have not been told that this is his normal bowel habit we might consider that it was caused by beginning obstruction of a growth in the colon. The anal pain at its onset is entirely consistent with an acute external thrombotic hemorrhoid, but its persistence is unusual in that condition and suggests some type of irritative process in the mucosa of the lower rectum.

Proctoscopic examination is consistent with an acute infectious colitis, even though the only ulceration is in the anal canal.

The blood picture and the specific gravity of the urine, if done the day of entrance, might be caused by the extreme dehydration; but, since we are told that they were a week after admission, it does prejudice us against the previous existence of malignant disease of any extent. This, taken with the later blood picture of a very considerable blood loss, makes us feel that we are dealing with a much more acute process.

What are the diagnoses that we have to consider? Malignancy of the large bowel; colitis, either tuberculous, amebic or idiopathic; and diverticulitis as a poor third. Against the first is the abrupt onset, the rapid course, the fairly normal blood picture on entrance, and the lack of any x-ray picture localizing a carcinoma. The mention of change in the pupils at first makes us wonder if a malignant metastatic nodule might have interfered with the cervical sympathetic chain, but this is not a true Horner's syndrome, and I think we can disregard it entirely. The lack of any localizing symptoms on abdominal palpation would rule out a diverticulitis, which would have to be rather severe and have to perforate to account for a chart and picture of this sort. I believe that on that basis alone it can be thrown out. This leaves us with colitis, and in a process as acute as this the most important evidence against tuberculosis is the negative chest x-ray. A chronic intestinal tuberculosis can be present without a background of pulmonary infection, but, according to the records in this hospital, the acute

process cannot. The suggestive large liver as indicated by x-ray might be in favor of amebic infection, but in an acute process microscopic examination should show the organism, and here it does not. This leaves us with acute idiopathic colitis and, as I see the picture, with the rapid course, the febrile chart, and the x-ray appearance of the large bowel, which is suggestive of colitis, I think that it is the only diagnosis we are justified in making.

At the age of this patient the prognosis is very poor in the acute type of colitis, and I believe the reason that ileostomy was not done was that because of the patient's poor condition the surgeon felt he would merely be making an antemortem examination. There are certain mild cases that will respond to appropriate medical treatment. We feel that the disease is primarily medical, and that a high vitamin, low roughage, high caloric diet with antispasmodic and sedative drugs will do as much for it as anything we know of at present. In the more severe type of case it may be necessary to do an ileostomy in order to put the whole large bowel completely at rest, but in such cases we feel that the ileostomy is preliminary in many instances to a later colectomy. There is also the type, as reported here, where no treatment known has any effect at all. My preliminary diagnosis is acute idiopathic ulcerative colitis.

Clinical Diagnoses

Acute ulcerative colitis.
Tuberculosis of the colon?

Dr. Edward L. Young's Diagnosis

Acute infectious colitis, idiopathic.

Anatomic Diagnoses

Colitis, ulcerative, acute generalized.
Pulmonary edema.
Hydrothorax, bilateral.
Cachexia.

Pathological Discussion

Dr. Benjamin Castleman: The autopsy on this man showed a moderate degree of small bowel distention. The cecum was also distended, but the only point of apparent obstruction was an acutely angulated sigmoid, which would fit in with the x-ray findings. The serosa of the colon had lost its glistening sheen but there was no frank peritonitis or evidence of perforation. The bowel, however, was very thin and friable and mere handling was sufficient to perforate it, a factor which should be borne in mind when attempting any surgery in the acute phase of ulcerative colitis. Dr. McKittrick has often stated how difficult and time-consuming it is to perform a colectomy on cases of ulcerative colitis, in contrast to the ease with which it is done, for example, in polyposis where the bowel wall is not involved. Scattered throughout the colon were numerous ulcers of varying sizes, some sharply punched-out and single, others shallow and confluent. One unusual feature of these ulcers was the distribution. Ordinarily the disease is much more severe in the rectum and sigmoid and becomes less extensive as one approaches the cecum, in contrast to tuberculosis in which the reverse is the rule. In this case, however, the most severe lesions were in the cecum, which was almost completely replaced by confluent ulcers. The ulcers decreased in frequency in the distal portions of the colon. Microscopically, in the regions of the ulcers, the mucosa has been completely denuded down to, and often through, the muscularis mucosa. The bases of these ulcers were covered with acute and chronic inflammatory elements and in several places cellular infiltration was present in the muscularis and pericolic fat. Numerous bacilli and cocci were present, but no amebae were seen.

The liver was slightly enlarged but at autopsy was above the costal margin. The spleen was small.

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CLINICAL LABORATORIES AND HORMONE TESTS

FOR the past ten years the Council on Medical Education and Hospitals of the American Medical Association has been active in an attempt to reduce the number of commercial laboratories under lay direction. Until 1931 an annual list of approved clinical laboratories was published, and since then individual pathologists and clinical pathologists have been certified according to a minimum standard of qualifications. The number of improperly supervised laboratories has decreased, but many still exist, owing undoubtedly, in part, to the patronage of physicians that are influenced more by the convenient location of the laboratory than by its qualifications and reputation.

With the increasing demand for hormone tests of pregnancy the need of sending specimens to a properly qualified laboratory is even more imperative than when the clinical laboratory was called upon to perform urinanalyses, blood chemistry determinations, basal metabolisms and the like.

Proper performance and interpretation of the Aschheim-Zondek test or the Friedman test are not always easy. All test animals must be of the proper age and the virgin doe rabbits used for the Friedman test should be kept in separate cages for at least two weeks prior to the test, unless the laboratory has facilities for breeding its animals or deals with that rare species of human being, a dependable animal man; this is a difficult problem. When the animal is sacrificed, the operator must be able to pass on the suitability of the animal and must repeat the test if the ovaries do not conform grossly, sometimes, even, microscopically, to the required standard. If borderline reactions are observed, there are several possible procedures. Histologic examination of stained sections of the ovaries, uterus and vagina of the infantile rat or mouse is frequently helpful. The injection of an alcohol precipitated concentrate may be indicated. In any case, the test should be repeated before a final report is given. All this requires knowledge and judgment that are rarely possessed by a lay director of a clinical laboratory.

Incorrect reports may lead to inexcusable therapy, ill-conceived operations, marital difficulties and even serious medicolegal complications. The responsibility rests on the physician, and he should be sure that specimens are sent only to laboratories that are properly qualified to perform and to interpret such tests.

ANNUAL REPORT OF THE COMMONWEALTH FUND

THE eighteenth Annual Report of the Commonwealth Fund, for the year ending September 30, 1936, records appropriations amounting to $1,967,153.26; the gifts being the largest since 1931. More than two thirds of the total sum were devoted to the betterment of health, with other grants made for public health service to rural communities, rural hospitals, medical education and medical research. Postgraduate education in medicine has been emphasized, as usual.

For the first time in several years, according to the Report, a large share of the appropriation went to educational institutions in New York City, the largest being a conditional gift of $250,000 to the College of Physicians and Surgeons of Columbia University, to meet part of the cost of enlarging laboratory facilities at the Columbia-Presbyterian Medical Center for graduate teaching in the medical specialties.

At the Babies Hospital and the New York Hospital, as well as at the Boston Children's Hospital, full-time psychiatric consultation has been provided for staff and students in pedi-

atrics. These grants are based upon the belief that a knowledge of child behavior and of emotional factors in children's diseases is an important asset in the medical care of infants and children.

In various ways the Fund has continued to work for the improvement of medical practice in rural areas, particularly in Tennessee, Mississippi and the northern New England states. Scholarships have been awarded for postgraduate study at Harvard, Tulane, Vanderbilt and other medical schools, and to undergraduates in medicine at Tulane, Vanderbilt and Tufts. According to the terms of the grants, twelve or more graduates will be ready each year for rural practice in Mississippi, Tennessee and Massachusetts.

The building of rural hospitals has been resumed; the seventh was opened a year ago in Kingsport, Tennessee, an eighth is nearing completion in Tupelo, Mississippi, and a ninth has been awarded to Ada, Oklahoma.

In the realm of public health, state health department service has been emphasized as the best means of improving local health work, and traveling units have supervised and strengthened local health departments in Tennessee, Mississippi and Massachusetts. The Nashoba Health District, centering in Ayer, Massachusetts, is now operating without subsidy from the Fund, and the other five will shortly be in the same position.

Appropriations have been made to the study of essential hypertension at Johns Hopkins University, of placental extract at the Harvard Medical School, of trachoma at Washington University, of rheumatic fever at the New York Hospital and the House of the Good Samaritan, Boston, of tuberculosis at Bellevue Hospital and the Harriet Lane Home in Baltimore, of kidney function at the University of Pennsylvania, of the chemical nature of insulin at Johns Hopkins University, and of growth and development in childhood at the University of Colorado.

Other activities have included studies in administrative care and legal history, fellowships for British graduate students at American universities, the training of psychiatrists and psychiatric social workers, and the publication of six new books having to do with public health, medicine, psychology and legal research.

THIS WEEK'S ISSUE

CONTAINS articles by the following named authors:

ZINSSER, HANS. M.D. Columbia University College of Physicians and Surgeons, 1903. Professor of bacteriology and immunology, Harvard Medical School. Address: Harvard Medical School, Boston. His subject is "Recent Advances in the Study of Typhus Fever." Page 449.

McKHANN, CHARLES F. M.D. University of Cincinnati College of Medicine, 1923. Formerly, visiting professor of pediatrics, Peiping Union Medical College. Now, associate professor of pediatrics and communicable diseases, Harvard Medical School and Harvard School of Public Health. Visiting physician, Infants' and Children's Hospitals. Consulting physician, Haynes Memorial Hospital for Communicable Diseases. Address: 300 Longwood Avenue, Boston. His subject is "Immunologic Application of Placental Extract." Page 450.

SMILLIE, WILSON G. M.D. Harvard Medical School, 1912. Formerly, interne and assistant resident, Peter Bent Brigham Hospital. Now, professor of public health administration, Harvard School of Public Health. Professor of preventive medicine and public health, Cornell University, 1937-. Address: 55 Shattuck Street, Boston. His subject is "The Epidemiology of Influenza." Page 451.

KEEFER, CHESTER S. M.D. Johns Hopkins University School of Medicine, 1922. Associate professor of medicine, Harvard Medical School. Associate physician, Thorndike Memorial Laboratory, Boston City Hospital. Address: Boston City Hospital, Boston.

SPINK, WESLEY W. M.D. Harvard Medical School, 1932. Assistant in medicine, Harvard Medical School. Resident physician, Thorndike Memorial Laboratory, Boston City Hospital. Address: Boston City Hospital, Boston. Their subject is "The Immune Reactions in Patients with Gonococcal Infections." Page 454.

SELLARDS, ANDREW W. M.D. Johns Hopkins University School of Medicine, 1909. Associate professor of tropical medicine, Harvard Medical School. Address: Harvard Medical School, Boston. His subject is "Immunization in Yellow Fever and Other Virus Diseases." Page 455.

ROBINSON, ELLIOTT S. M.D. Yale University School of Medicine, 1918, Ph.D. 1922. Director, Division of Biologic Laboratories, Massachusetts Department of Public Health. Assistant professor of applied immunology, Harvard Medical School and Harvard School of Public Health. Address: 375 South Street, Jamaica Plain. His subject is "The Antiserum Treatment of Pneumonia from the Standpoint of Public Health." Page 459.

FINLAND, MAXWELL. M.D. Harvard Medical School, 1926. Instructor and Francis Weld Peabody Fellow in Medicine, Harvard Medical

School. Assistant physician, Thorndike Memorial Laboratory, Boston City Hospital. Address: Boston City Hospital, Boston. His subject is "Some Aspects of Pneumococcus Infection in Man." Page 460.

STRONG, RICHARD P. M.D. Johns Hopkins University School of Medicine, 1897. Sc.D. Yale University (Honorary), 1914. S.D. Harvard University (Honorary), 1916. Professor of tropical medicine, Harvard Medical School. Consultant in tropical diseases, Boston City and Massachusetts General Hospitals. Member, Massachusetts Public Health Council. Address: Harvard Medical School, Boston. His subject is "Studies on Filarioidea." Page 461.

AUGUSTINE, DONALD L. Sc.D. Johns Hopkins University, 1923. Assistant professor of helminthology, Department of Comparative Pathology, Harvard Medical School and Harvard School of Public Health. Address: Harvard Medical School, Boston. His subject is "Trichinosis—Incidence and Diagnostic Tests." Page 463.

PINKERTON, HENRY. M.D. Harvard Medical School, 1924. Assistant professor of pathology, Harvard Medical School. Address: Harvard Medical School, Boston.

HASS, GEORGE M. M.D. Harvard Medical School, 1929. Instructor in pathology, Harvard Medical School. Junior Fellow, Harvard University. Address: J 31, Winthrop House, Cambridge. Their subject is "The Study of the Pathogenic Rickettsiae in Tissue Culture." Page 466.

BURGESS, ALEX. M. M.D. Harvard Medical School, 1910. Visiting physician, Rhode Island Hospital. Physician-in-chief, Medical Department, Charles V. Chapin Hospital, Providence. Chairman of the Division of University Health, and assistant professor of biology, Brown University. Address: 454 Angell Street, Providence, R. I. His subject is "Oxygen Therapy: A Modification of the Box Method for Giving 95 Per Cent Oxygen." Page 467.

SMITH, F. J. C. M.D. Harvard Medical School, 1932. Formerly, senior medical officer, Passamaquoddy Tidal Power Project, Quoddy Hospital, Quoddy, Maine. Now, assistant physician, State Prison Colony. Address: State Prison Colony, Norfolk, Mass. His subject is "Traumatic Intraperitoneal Rupture of the Bladder." Page 469.

The Massachusetts Medical Society

SECTION OF OBSTETRICS AND GYNECOLOGY*

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CASE HISTORIES

No. 11. CHORIO-EPITHELIOMA

Mrs. L., a white woman, aged 49 years, was referred by her family physician to the Gynecological Service of the Carney Hospital on June 13, 1936. She stated that her last regular menstrual period was April 27, 1936. During the last week of May slight staining was noticed, and early in June she began to flow, using from three to six napkins a day. Some nausea with occasional morning vomiting had been experienced for the last month.

The family history disclosed no tuberculosis, diabetes or malignancy. The patient's health had been excellent since childhood. The only illnesses were influenza in 1919 and an operative excision of a varicose vein of the leg 20 years ago. She had been married 12 years, and her husband and two children were living and well. The pregnancies were normal, with spontaneous delivery at term and the puerperia were uneventful. Her third pregnancy terminated in a complete miscarriage 5 years ago. Catamenia, which began at the age of 13, had a 28 day interval and lasted 4 to 5 days. Except during pregnancy they had always been regular and normal.

On physical examination the patient was tall and well-developed with good color of the face and mucous membranes. The temperature was 99.2°F. There were some dental cavities, but the throat and buccal mucosa were normal. The chest was symmetrical with normal resonance and breath sounds and no rales. The heart was of normal size, the sounds were regular and of good quality, and there were no murmurs. The blood pressure was 112 systolic, 72 diastolic; the peripheral vessels were soft; and the pulse rate was 90 per minute. The breasts were pendulous with some increased pigmentation of the areolae. A symmetrical, smooth, nontender mass could be felt three fingers above the symphysis pubis. Vaginal examination under aseptic precautions disclosed moderate relaxation of the perineum and a slight bloody discharge. There were hypertrophy and bilateral laceration of the cervix. The uterus was firm, in good anterior position

*A series of selected case histories by members of the Section will be published weekly.

Comments and questions by subscribers are solicited and will be discussed by members of the Section.

and the size of a 4 months' pregnancy. There were no masses or tenderness in the vaults. The reflexes were somewhat hyperactive, and moderate varices of the legs were present.

Blood examination showed: red blood cells 4,100,000, white blood cells 6,870, hemoglobin (Sahli) 80 per cent. The urine contained a slightest possible trace of albumin but no casts. On June 16, the Aschheim-Zondek test was positive.

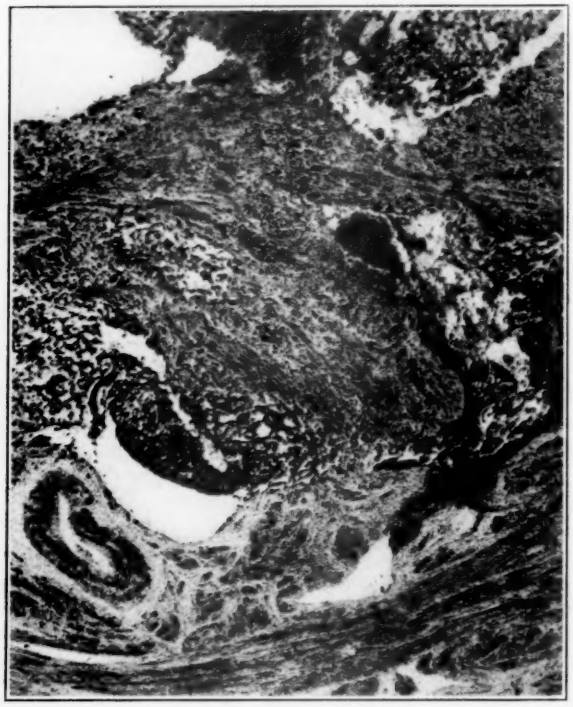

FIG. 1. Low power. Tumor on endometrial surface with invasion of adjacent smooth muscle. Small mass of tumor in vessel fairly deep in myometrium.

The following day, June 17, profuse flowing started, and a hydatidiform mole, the size of a full-term placenta, was expelled. Ergot and pituitary extract were administered, but the flowing continued. Under aseptic precautions the uterine cavity and vagina were firmly packed with 2-inch iodoform gauze. June 18 the pack was removed, and the remaining pieces of mole were carefully extracted from the uterine cavity. The latter was then gently explored with the gloved finger and found to be completely evacuated. Pituitary extract and ergot were repeated, the uterus contracted well, and there was very little bleeding.

The pathologist's report was as follows:

"Pathological ovum, group I (Carnegie classification). Hydatidiform mole, probably benign, showing hyperplasia and slight anaplasia with slight tissue-culture-like growth of epithelium on decidua and blood clot. Possible persistent mesogenesis."

Convalescence was uneventful. The pulse and temperature remained normal after the second day and the slight flow ceased entirely on the fifth day. On June 26 the uterus was firm, well-involuted and in good anterior position. The patient was discharged after being told that close observation for several months and further treatment might be necessary.

On July 27, she reported at the Carney Outpatient Department for a check-up. There had been no pain or flowing, and the patient felt very well. There was no discharge from the cervix; the uterus was very little larger than normal, firm, nontender and in good anterior position. There were no masses or tenderness of the vaults. A specimen of urine was sent to the laboratory. *The rabbit test and rat tests were positive.* A 24 hour specimen of August 1 and 2 contained 10,000 rat units of prolan A per liter, or 4,600 rat units per 24 hours, and 5,000 rat units of prolan B per liter, or 2,300 rat units per 24 hours.

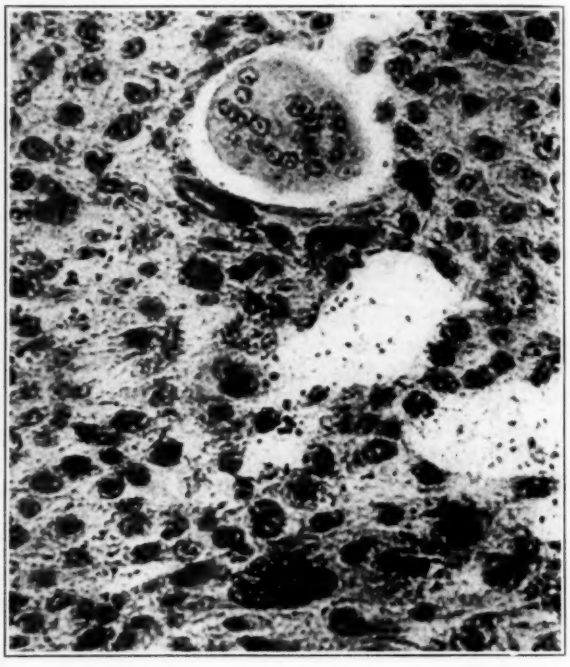

FIG. 2. High power. Tumor composed of two types of cells—syncytial masses and Langhans's cells. One large tumor giant cell present.

The patient was readmitted to the Carney Hospital, and on August 1 a panhysterectomy with bilateral salpingo-oophorectomy was performed. The patient made an excellent recovery and was discharged August 14. Urine collected on that date gave a *negative* Aschheim-Zondek reaction.

The pathological report was as follows: "The tumor is made up of two types of cells—a mononuclear cell corresponding to the Langhans's cells, and a multinucleated cell of the syncytial type. In places the Langhans's type cell is small

and apparently well-differentiated, but mitotic figures are numerous and often atypical. For the most part, however, the cells are large and atyptical in character. Sections through the wall of the uterus show the tumor definitely invading the wall, apparently growing into the veins. Diagnosis: chorio-epithelioma."

On August 29, the patient was examined in the Outpatient Department. There were no symptoms, the vagina was normal, the vaginal vault high and there were no pelvic masses or tenderness. The Aschheim-Zondek test was again negative.

Bi-monthly examinations have revealed no pathology, and the patient has continued to be symptom-free 5 months after operation. Aschheim-Zondek tests at monthly intervals have all been negative. As chorio-epithelioma usually grows more rapidly than any other type of neoplasm, causing death in 3 to 5 months, and because treatment was instituted so early in the case, it is reasonable to assume that this patient is cured. However, the monthly examinations and Aschheim-Zondek tests will be continued until a year or more has elapsed since operation.

Comment: It is fair to assume that the Aschheim-Zondek test saved this woman's life. Chorio-epithelioma is the most rapidly growing of all malignant tumors, and death from extensive metastases may result in 3 to 4 months in untreated cases after the onset of the disease. If the diagnosis is not made until clinical signs and symptoms appear, it is usually too late. When, after the expulsion of a hydatidiform mole, the urine test becomes negative, and then becomes positive again in a few weeks, a new pregnancy should, of course, be considered. This is easily distinguished from malignancy by quantitative Aschheim-Zondek tests, which will show a markedly increased amount of gonadotropic substance when chorio-epithelioma is present.

MISCELLANY

TUFTS COLLEGE MEDICAL SCHOOL

Dr. Dwight O'Hara, professor of preventive medicine, has been named vice-dean. Dr. O'Hara is also councilor of the Middlesex South District of the Massachusetts Medical Society and was chairman of the Committee on Public Health for the years 1928 and 1936 and of the Committee of Arrangements for the year 1925. He served as a member of the Massachusetts State Health Commission in 1935 and 1936.

Dr. John Martin Wheeler, professor of ophthalmology, Columbia University, spoke before the William Harvey Society on March 5. His talk on "Various Types of Grafts Used in Plastic Surgery about the Eyes" was beautifully demonstrated by illustrations of a great number of successful cases.

Dr. Walter B. Cannon, professor of physiology, Harvard Medical School, spoke at the request of the William Osler Student Honorary Society, March 16, on "The Nature of Emotional Behavior."

Dr. James B. Collip, professor of biochemistry, McGill University, will lecture before the Harvey Society April 16. A pioneer and authority in the field of endocrines, Dr. Collip will speak on "The Significance of Recent Studies upon the Anterior Pituitary and Related Glands."

A local chapter of the American Association of Medical Students has been formed. It will submit its constitution for inclusion in the Students' Activities Plan of the medical school.

ATTITUDE OF ANESTHETISTS TOWARD HOSPITAL SERVICE PLAN

In the issue of *The New England Journal of Medicine* of November 26, 1936, there was published a resolution unanimously adopted at the November meeting of the Boston Society of Anesthetists to the effect that anesthetists and the administration of anesthetics should not be included in the hospital service plan.* A more amplified statement of the attitude of the Boston Society of Anesthetists toward the plan seems to be needed.

The hospital service plan appears to be an insurance method of making hospital bills easy for the patient to pay. The benefits do not include the services of the attending physician and surgeon. It has been proposed, however, that laboratory and pathological services, ordinary x-ray examinations and anesthesia be included in the benefits. The pathologists appear ready to have their services included, but the roentgenologists have stood firmly against the inclusion of their services. It is obvious that the plan is primarily intended to cover hospital services, and not physicians' services.

There are three types of relation of anesthetists to such hospital service corporations. In the first type the insuring corporation agrees to pay to the hospital a certain amount for each anesthesia administered to subscribers. It is important to note that this sum is to be paid to the hospital, not to the anesthetist. The hospital may then do whatever it decides with the money. It may turn over to the anesthetist the full amount received or it may turn over any fraction of that amount. This plan might therefore tend toward price-cutting between anesthetists, with the hospital giving its work to those with whom it could make the most favorable financial arrangements; or the hospital would be at liberty to employ an anesthetist or a lay technician, pay to that person a low salary, such as one hundred to two hundred dollars a month, collect from the hospital service corporation from five to twenty

*The resolution adopted was: "Resolved: that it is the sense of this Society that the hospital prepayment plan as at the present drawn up would, if the anesthetists should be included, tend to reduce them toward the position of technicians, would tend to place them under the control of the hospitals and would set them apart from other branches of medicine; that these influences would tend to stop progress in anesthesia and to push the practice of anesthesia back to its status of a few decades ago, and would ultimately result in poorer service to the patient; and that for these reasons the Society stands against being included in the contract as now proposed."

dollars for each anesthesia administered, and keep the difference. Thus, financial control of anesthesia would pass from the hands of the medical profession to the hospitals, and with it clinical control also would be likely to pass.

The second plan is that proposed for the Hospital Service Corporation of Boston. No separate fee would be paid by the corporation to the hospital, but the corporation would pay to the hospital a set amount, probably between six dollars and ten dollars a day, for each subscribing patient, and from this amount the hospital would meet the expenses of eight specified services, "including anesthesia when administered by a suitable, salaried employee of the hospital". This would tend to drive physicians entirely from the field of anesthesia so far as subscribers to the hospital service plan are concerned. Any hospital that did not furnish anesthesia would be at a disadvantage in that the subscribers who had paid for anesthesia when paying their insurance premiums would choose to go to the hospitals where that service was furnished; and any hospital attempting to furnish physician anesthetists to subscribers might be at a financial disadvantage as compared with hospitals which furnished the cheaper services of lay technicians. Anesthesia would thus pass from the hands of the medical profession and would become a hospital service in company with nursing care, orderly care, diet and drugs.

The second plan, that proposed for the Hospital Service Corporation of Boston, is by far the more objectionable of the two. The first plan was put into effect in Rochester, New York; but at the end of one year it was dropped, and the second plan was put into effect without consulting the anesthetists. The service corporation under the second plan paid six and one-half dollars per patient per day to the hospitals, for which amount the latter furnished ordinary hospital care, anesthesia, electrocardiograms, basal metabolism tests, laboratory work, and so forth. They were asked by the anesthetists to drop anesthesia from the plan, but *the four hospitals that used lay technicians refused to do this because they were making money from anesthesia.* It is, therefore, evident that under a plan similar to that proposed for Boston, anesthesia has passed from the hands of the medical profession and has become a hospital service rendered by lay technicians.

The third plan is that which is sponsored by the Boston Society of Anesthetists and which is said to be enforced by the Hospital Service Association of New Orleans and the Hospital Service Corporation of Washington, D. C. It keeps the anesthetist in the same relation to the patient that holds for the internist, the surgeon, the pediatrician and other consultants. From the sample contracts drawn up for the Hospital Service Corporation of Boston the phrase "including anesthesia when administered by a salaried employee of the hospital" should be stricken out, and the phrase, "it shall not include the professional services of patients' attending physicians and/or surgeons", should be extended to include anesthetists. The anesthetist's bill should be sent to the patient just as are those of the rest of the medical profession.

It is the feeling of the Boston Society of Anesthetists that under the first two plans it would be financially advantageous for hospitals to furnish lay technicians in anesthesia; that patients and surgeons would not have a free choice of anesthetists unless the patients were to pay a second time for anesthesia service; that price competition between physicians and lay technicians would be accentuated; that anesthesia would gradually pass from the control of physicians to the control of hospitals; and that this condition would tend to halt the progress in anesthesia that has been so noteworthy in the last decade. The Society also feels that the administration of anesthetics is the practice of medicine and that, therefore, it is not a suitable service for hospitals to sell or for lay technicians to practice. The Society further feels that there is no reason why the bill of a physician who administers an anesthetic should be handled through a service corporation and a hospital, while the bills for other types of professional services, whether rendered by the same physician or by others, remain a private matter between the physician and the patient.

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SCHOLARSHIPS AND FELLOWSHIPS AT THE HARVARD MEDICAL SCHOOL

Twenty-five scholarships and fellowships have recently been awarded to students at the Harvard Medical School. Seven of the awards went to Massachusetts students. The stipends of the grants total $7,325.

BUILDING PROGRAM PROPOSED FOR BOSTON STATE HOSPITAL

A building and renovating program for the Boston State Hospital at Mattapan, and the employment of 100 additional attendants are recommended in the report to be filed in the House of Representatives' Ways and Means Committee by Dr. Harold F. Norton, superintendent. The report was approved by Miss Josephine E. Thurlow, chairman of the newly appointed board of trustees of the hospital, and is now being studied by the state budget commissioner.

The report recommends a $1,000,000 building pro-

gram, in addition to the expenditure of $1,110,500 for renovating the institution and furnishing equipment for patients and members of the hospital staff. Dr. Norton has also requested a $360,000 appropriation for food.

CORRESPONDENCE

CONCERNING HOUSE BILL 1200

February 24, 1937.

Editor, *New England Journal of Medicine,*

When, in the past, appeals have been made to physicians in matters affecting the public welfare they have been answered, as in the manner of today, with the utmost cooperation and without reference to any possibility of future self-sacrifice on our part.

I believe that it was more because of this policy than for any other reason that few of us were willing in Council assembled to oppose a certain measure under consideration, namely, that the Massachusetts Medical Society through its Council recommend the adoption of proposed legislation to place within the jurisdiction of the Massachusetts Department of Public Health the care and treatment of a number of cases suffering from chronic illness. I think that many of us somewhat reluctantly allowed ourselves to decide that since our position had again been challenged, we should once more express our magnanimity in a practical way, that we might not again be accused of having been activated by selfish motives; but when is the end?

To question whether the functions of health boards properly include jurisdiction over cases other than those afflicted with contagious or communicable disease is not the purpose of this writing. The purpose is to inquire into the reasons why such extension of privileges is deemed necessary, to review some of the pertinent facts, and to offer for consideration a few of the merits of a substitute plan for the care and treatment of all the sick poor under our own supervision. The inquiry is applicable not only to privileges extended to boards of health that have only recently entered this field of endeavor, but to all institutions concerned in the operation of free and part-pay clinics for the care and treatment of the sick.

The answer to this inquiry is found not solely in connection with the particular measure with which the Council was on this day concerned, but more generally in the fact that sick poor have required the services of physicians throughout the years and that no better or equally satisfactory methods have been devised to supply this care than those now in vogue. No plan has been evolved to provide for such need under the auspices of those next nearly concerned, either by the physicians themselves, or, in particular, by their representative organization, the Massachusetts Medical Society.

I feel certain that no difficulty would have been encountered in the Council meeting of today in obtaining the unanimous opinion that the Massachusetts Medical Society is well fitted, from the standpoint of professional attainment, to cope with such chronic cases. Nevertheless these cases are being referred in constantly increasing numbers to other agencies for care. I feel equally certain that no member of our Society places fees above the interest of his patients either in his first or in his final evaluation of the matter. On the contrary, I am impressed that, in the light of his knowledge and experience, the physician fears, in the interest of his patients as well as of himself, the result of decreased interest in, and decreased potentialities for, practice and research, because of the process of thinning of the ranks of the trained. This is bound to ensue if the income of all physicians, except those of the salaried group, is systematically reduced by any means whatsoever to a level which may not assure even a fair living in return for a given effort. Work and wages are inseparable under our present standards. Progressive reduction of the latter can but tend to undermine and eventually destroy our entire present system of medical practice.

Whether or not all of the above premises can be accepted, the question still arises as to what the Massachusetts Medical Society is going to do about the whole broad problem of charity and part-pay clinics in the practical interest of the public welfare as well as in the interest of its members. Was our action of today a tacit admission that the Society cannot or will not provide, except through the medium of extraneous agencies, for a need that our legislators will meet whenever it arises whether we approve their methods of provision or not? Shall the Society continue to permit these agencies virtually to dictate policies for the Society's approval but for their own management? If so, how long can the Society maintain its present high standard of respect and its equally important position as the last authority in matters medical?

However wise our predecessors in this Society were, and I believe that they were wise, they failed to exercise a degree of foresight sufficient to obviate the predictable status in which we, their successors, find ourselves today. Now that the situation is the more obvious because of its presence among us, are we not the more to blame for continued inaction? Shall we remain in status quo or shall we look ahead?

I am fully cognizant of the fact that problems which seem insurmountable, or which will be held so to be, loom large before the institution of any new plan. Nevertheless, I feel certain that, if the Society in the years that have passed had organized clinics for the care of the poor under its own auspices and had operated them in the various municipal and suburban districts under the direction of the district societies, the problems of both the sick poor and those of the physician would by now have been solved.

Any such plan would need to contemplate and to observe the principle: "Every fellow a visiting

physician subject to his choice." Adherence to this principle would need to be held and to be kept inviolable. Reasonable expectation of the production of the following results might then be anticipated: stimulation of the interest of a very large number of physicians who possess no clinic privileges under our present system; extension of the field of individual practice and experience; increased potentialities for the promotion of research. All of these would be of direct benefit to the patient and of indirect benefit to the physician. The plan would work against the abuse of medical charity by placing local cases under the care of local physicians. These physicians best know the economic status of these individuals and could best decide what fee might fairly be contributed by them toward the operative cost of the organization. This would be of direct benefit to both.

Those who sponsored House Bill 1200, Appendix 48, in the Council meeting, desired us to provide a better plan or accept the measure proposed. If there is need for this service then they were right, but considering the matter in its broadest applications, should we not look forward to the formulation and to the adoption of a better plan?

Yours very truly,

FRANK S. CRUICKSHANK, M.D.

1247 Beacon Street,
Brookline.

ANESTHETISTS IN RELATION TO THE HOSPITAL SERVICE PLAN

Editor, *New England Journal of Medicine*,

In the present issue of this *Journal* appears a statement as to the attitude of anesthetists toward the Hospital Service Plan. This plan involves the collection by the hospital of an anesthetist's fee and would, I believe, result in very definitely lowering the standard of anesthesia. It would and has encouraged hospitals to employ nonprofessional anesthetists at limited salaries, because from this accumulates a profit to the hospital.

The progress in anesthesia within the last few years has been most satisfactory, and it has definitely been related to permitting anesthetists to acquire standing as individuals and to be remunerated in proportion to their worth.

Such a plan as suggested, whereby a fee for anesthesia is included in a lump sum payment collected by the hospital, would tend very seriously to return anesthesia in the direction of the depths from which it has arisen.

No one who has had any extensive experience with the modern developments in anesthesia can have failed to be impressed with the fact that these developments have made surgery infinitely easier for the surgeons and infinitely easier and safer for the patients. It would be a pity to include anesthetists under the same heading as technicians and discourage progress already well under way.

FRANK H. LAHEY, M.D.

605 Commonwealth Avenue,
Boston.

RECENT DEATHS

CARUSO—SEPTIMIO CARUSO, M.D., aged 44, died December 24, 1936, in St. Elizabeth's Hospital, Boston.

Dr. Caruso graduated from Tufts College Medical School in 1918, and joined the Massachusetts Medical Society the same year.

WATTERS—HENRY WATTERS, M.D., of 47 Grafton Street, Newton Center, died at his home, February 19. He was in his fifty-sixth year.

A native of Melbourne in the Province of Quebec, Dr. Watters was graduated from St. Francis College at Richmond, Quebec, and came to the United States for his medical training. He was graduated from the Boston University School of Medicine in 1905, after which he served as an intern at the Newton Hospital, and at the end of his internship was appointed a member of the surgical staff. During recent years he had served the hospital as a trustee and as a member of the executive committee. From 1905 to 1914 he was associated with Dr. George E. May of Newton Center.

Organizations in which he held memberships include the Massachusetts Medical Society, the American Medical Association, the Massachusetts Homeopathic Society, the Newton Medical Club, the Rotary Club and the Masonic Order.

He is survived by a brother, Malcolm Watters, of Kingsbury, Quebec, and four sisters, Miss Anne Watters with whom he made his home, Mrs. Louis Harris, of Valoris, Quebec, Mrs. Samuel Scott, of Scotstown, Quebec, and Mrs. Earle Simes, of Kingsbury, Quebec.

CAULFIELD—THOMAS EDWARD CAULFIELD, M.D., of 14 Church Avenue, Woburn, died at his home, March 8. He was in his fifty-eighth year.

Having received his early education in Woburn public schools, Dr. Caulfield was graduated from the Harvard Medical School in 1902. He served his internship at the Carney Hospital, and began general practice in Woburn in 1903. During the World War he was commissioned a captain and served with the medical corps. He was chief surgeon at the Choate Memorial Hospital and a former city physician of Woburn.

Organizations in which he held memberships include the Massachusetts Medical Society, the American Medical Association, the New England Obstetrical and Gynecological Society and the Woburn Medical Association.

He is survived by his widow, a son, Dr. Thomas E. Caulfield, Jr., and a daughter, Jeanne.

OBITUARIES

DR. WILLIAM B. KEELER

The people of Boston, the personnel of the Boston Department of Health, and all of his many friends, sustained a great loss in the passing of Dr. William

B. Keeler, health commissioner of Boston for a period of a little more than a year.

Dr. Keeler was engaged in the practice of medicine for more than a third of a century. He was a member of the Department of Health for about fourteen years, serving in the capacity of medical inspector, district health officer in South Boston, and director of the health unit located in that section of the city, and then as health commissioner. He was one of the most widely known physicians in New England. Genial, courteous, affable, he added to his friendships almost every day of his useful life. As director of one of the eight health units made possible by the George Robert White Fund, he made his unit in South Boston one of the most popular in this chain of widely used municipal buildings.

He was born in Schenectady, New York, in 1877, but was brought by his family to Boston when he was but two years old. A graduate from the Boston English High School and from the Tufts College Medical School in 1903, he served an internship at the Boston City Hospital. He was a senior member of the visiting staff of the Children's Department at St. Margaret's Hospital. He was a member of the American Medical Association, the Massachusetts Medical Society, and the Tufts College Alumni Association; past president of the Norfolk District Medical Society; honorary president of the Boston Health League; a member of the United States Public Health Service, and the Massachusetts Catholic Order of Foresters.

During his brief tenure of office as health commissioner, he established most definitely in the minds of those interested in public health progress in our city the facts that he was not only most competent to serve in the important position that he filled but that it was his intention to interrelate the service of the Boston Department of Health with the very valuable activities of the private agencies which concern themselves with health and relief.

Dr. Keeler will be missed by the many who were privileged to call him friend, and all who knew him join in extending sincere and heartfelt sympathy to his wife and daughter, as well as to the more distant members of his family.

C. F. W.

MEMORIAL TO THE LATE DR. FRANCIS J. NASH

On Monday, January 11, 1937, occurred the death of Dr. Francis J. Nash.

Dr. Nash was one of the organizers of the West Roxbury Medical Association and on its inception became its first treasurer, relinquishing this office only after he had convinced us that, on account of the pressure of his many duties, he could no longer conscientiously serve in that capacity. His presence at our meetings was always greatly desired as his straightforward manner of approaching a subject, together with his sagacity and humor, never failed to make the topic under discussion more interesting and instructive.

This association deeply regrets his early demise, feeling his loss not only for itself but for our entire community.

Therefore: Be it resolved that this testimony be incorporated in the records of the West Roxbury Medical Association and a copy of the same be transmitted to his widow, Mrs. Geraldine S. Nash.

For the Association:

NORMAN A. WELCH,
HERBERT L. JOHNSON,
M. WINTHROP O'CONNELL.

MATTHEW VASSAR PIERCE, M.D.

AUGUST 6, 1855 - JANUARY 24, 1937

Matthew Vassar Pierce was born August 6, 1855, on Green Street in the West End of old Boston, and received his early education at the Boston Latin School. He entered Harvard College with the class of 1877, numbering among his classmates Charles Sumner Bird, Charles K. Cobb, William Farnsworth, Amory Eliot, John Lowell, Barrett Wendell and A. Lawrence Lowell. After graduation, he, with two of his most intimate friends, Gardner W. Allen and Hayward W. Cushing, matriculated at the Harvard Medical School, from which he graduated with the class of 1880. At the medical school he was associated with William N. Bullard, Harold C. Ernst, Henry P. Jaques and George H. Monks.

The medical school of those days was on North Grove Street, near the Massachusetts General Hospital. Oliver Wendell Holmes was professor of anatomy. Henry J. Bigelow occupied the chair of surgery and John P. Reynolds was teaching the art and science of midwifery. Reginald Fitz was beginning his investigations in pathology and was yet to identify appendicitis; both pathology and physiology, under Henry P. Bowditch, were in their formative stages, largely influenced by the German school of thought. Microscopy was practiced in a rudimentary way, although Koch had not yet discovered the bacillus of tuberculosis, nor was the Klebs-Löffler bacillus known. Obstetrics was practiced under cover, almost literally, to protect the modesty of the mother, while sepsis and laudable pus were terms in common usage and abundantly in evidence. Medical wars were inaugurated shortly after this period, and these still persist in lesser degree on the relative values of chemical antiseptics.

Nothing was known of bacterial and protozoal diseases, blood diseases, or abdominal, neurologic, thyroid, or chest surgery; certainly the metabolic diseases were a closed book, while roentgenology and blood chemistry were far in the future. Laënnec had stimulated the diagnosis of chest diseases by the introduction of the stethoscope, but, aside from that one diagnostic instrument, the student had little to aid him beyond his God-given and man-trained five senses. It almost seems in retrospect as though morphine, potassium iodide, emetics, cathartics, a knife and common sense were the doctor's armamentarium in this era.

On the day after Dr. Pierce received his degree of doctor of medicine, he married Margaret Gray

Whitten, and they immediately sailed for Europe where he was to continue his medical studies in the clinics of Berlin, Heidelberg and Vienna, then the famous medical centers.

Returning in 1882, after two years of work, he chose to settle in Milton, where, for nearly fifty-five years, he remained an active and successful practitioner. We may well marvel at his innate ability which allowed him, with so rudimentary a training, though it was the best of the day, to continue to keep abreast of the revolutionary advances in medicine throughout these years.

Milton, in those days, was largely a rural district. Its people were highly conservative, and most of the houses were far apart and scattered over a wide area. Dr. Pierce told, in later years, gleefully his story of seeking an office and, having heard of one, the only possible one apparently, of applying for it only to find that the day before another doctor had engaged it. And so it was with living quarters in the only boarding house in town! However, with his natural buoyancy and courage, these obstacles were overcome and he started in general practice, which continued to grow so that he was unable to relinquish it even if he had so wished. In those early days he almost lived in a two-wheeled gig, which night and day carried him on his merciful errands. His skill gained for him an enormous obstetric practice, most of which was accomplished in the homes of his patients, whether rich or poor. His genial cheeriness, kindliness and common sense won him a place in the hearts of his patients that no one else can fill. He joined the old Dorchester Medical Club in 1882, with such bon vivants and medical giants as Ellery Stedman, Orville Rogers, Christopher Columbus Holmes, Benjamin Cushing, Henry Blanchard and W. C. B. Fifield. He lived to participate in a dinner given in his honor fifty years later, which a number of Boston medical celebrities attended and to which he was willing to come only if no mention was made of him! Endowed with discrimination, a constant student and reader of medical literature, ripened by his years of experience and observation, his medical contributions were timely and constructive. This club was his constant love, to which, as was usual with him, he gave much more than he could have possibly received.

He had a most self-effacing modesty as is evidenced by his repeated assertion that if a patient left him for another doctor, it was because of some fault of his own. His humor was spontaneous, contagious and apropos. Never did an occasion arise in which he was at a loss for a story and he was sure that many times his stories had helped the patient more than his pills. Some of us remember hearing him speak of psychotherapy when it first became fashionable, and of his experience with it as applied to a disgruntled couple, whom he sent to a psychotherapeutist and who told him that he had given them a "mental spanking" for their good. On thinking it over, it occurred to Dr. Pierce that he could do that just as well and at less expense to the couple, so on the next occasion he went to the home and administered the remedy. To his great surprise "they both got mad and threw him out of the house." He concluded that psychotherapy was not in his line.

Dr. Pierce was charitably inclined beyond most men, giving largely of his time and substance to worthy causes. In 1903 he established a convalescent home in Milton, which two years later was enlarged to include hospital facilities, with himself as chief-of-staff. It is now an improved institution, a monument to his charitable enterprise.

He was a member of the Unitarian Church in Milton, which he attended regularly and where his counsel was sought on important matters. He was one of the founders and a director of the Milton Savings Bank, and a director of the S. S. Pierce Co.—honors that he modestly accepted as a duty. His home life was exceptionally happy and was blessed with four children, one of whom died as a small child from poliomyelitis, and in whose memory he was accustomed to give a birthday party each year for poor children.

To a notable degree Dr. Pierce was a home-loving man, rejoicing in the companionship of his wife and children and in his later years devoting himself to his grandchildren. In 1930, at the time of Dr. and Mrs. Pierce's golden wedding anniversary, nearly the whole town was invited to gather at their home in friendly and neighborly fashion to celebrate the occasion, which carried the conviction that never had one found a couple more deserving of the appellation "worthy," with their radiance of warm welcome, good cheer and happy youthful spirit.

To one who knew Dr. Pierce for over thirty-five years, the total absence in his make-up of such baser emotions as envy, jealousy, malice and hatred was impressive. He could and did express himself forcibly and positively when the occasion demanded, but never did rancor or bitterness appear. He was quick to laud the honors his contemporaries received, to applaud their successes and to praise their accomplishments whole-heartedly and with a graciousness that carried a warmth of feeling directly from his heart to the recipient's. But of his own accomplishments he was modest to a degree that was almost embarrassment.

When a man is a great man in the life that he lives, there are necessarily so many angles and facets that are rounded into the whole that one merely glimpses parts of the structure. Every part of his life was exemplary, helpful and generous to all with whom he came in contact. So many times we have heard him exclaim, "I never learned the art of medicine" and "I am not scientific," yet his art was supreme, founded as it was on love and charity, while his sense of science was so great an urge that in the later years of his life he made an intensive study of diseases of the blood.

Dr. Pierce was president of the Norfolk District Medical Society from 1915 to 1916, and for a number of years was a councilor of the Massachusetts Medical Society.

He was a man of courage in meeting life as it came, being fully aware that the ending is just as integral a part as is the beginning. He would not have wanted grief at his passing, being as unafraid of death as he was of life, and wishing to leave as he entered, unheralded and unsung except in the hearts of those who loved him.

A true gentleman, an exemplary doctor of the old school, a beloved member of this Society, we salute you.

W. A. L.

REPORTS OF MEETINGS

NEW ENGLAND HEART ASSOCIATION
MARCH 8, 1937

Studies on the Use of Prontylin in Rheumatic Fever

BY BENEDICT F. MASSELL, M.D.

Recently a good deal of publicity has been given to a drug which is said to be effective in the treatment of diseases caused by the hemolytic streptococcus. This substance is para-amino-benzene-sulfonamide, but it is popularly known under the trade name of "prontylin".

Because of the close relation of rheumatic fever to hemolytic streptococcus respiratory infections, a study of the effect of prontylin on patients ill with rheumatic fever seemed warranted. Such a study has begun. Although the number of cases to date is far too few to allow even tentative conclusions, certain observations seem of sufficient interest to report at this meeting.

1. Because of the well-known frequency with which rheumatic fever recrudescences follow upper respiratory infections, the prophylactic effect of prontylin has been tested. During the past 2 months twelve rheumatic fever patients have had upper respiratory infections with which there has been an associated positive throat culture for hemolytic streptococcus. Six of these patients were given prontylin and the other six served as controls and were given aspirin. Of the prontylin cases, two developed a recrudescence of rheumatic fever and one died, and of the aspirin cases, two developed a recrudescence of rheumatic fever and one died.

The appearance and course of the throat infection itself were comparable in the two groups, except that those who received aspirin were more comfortable. The duration of positive throat cultures for hemolytic streptococci varied from 2 to 44 days and averaged 16 days for the prontylin group, and 18 days for the aspirin group. Each group contained one patient who developed cervical adenitis as a complication.

2. Prontylin was also given to two patients with frank rheumatic fever, and to two patients with active chorea. In no instance was any beneficial effect observed.

3. In addition to the cases already mentioned, four other patients have been given prontylin, making a total of fourteen who have received the drug. Four of these developed a marked maculopapular rash which disappeared when the drug was discontinued and reappeared when it was again given.

One patient during the period of prontylin administration developed a leukopenia of 3,700. The drug was immediately discontinued and the leukocyte count gradually rose to its previous level of 8,000 to 10,000.

The following papers were also presented at the meeting; as these papers report work which is completed and will shortly be published in detail in other scientific journals, it was decided not to print summaries of this work at the present time:

A Course of Rheumatic Fever and Heart Disease: A Fifteen-Year Study. Edward F. Bland, M.D.

The Incidence of Recurrences of Rheumatic Fever. John P. Hubbard, M.D.

Clinical Analysis of Recurrences of Rheumatic Fever in Relation to Precipitating Events. T. Duckett Jones, M.D.

Hemolytic Streptococcus Studies in Rheumatic Fever. John R. Mote, M.D.

Short Summary of Virus Studies. T. Duckett Jones, M.D.

THE MASSACHUSETTS PUBLIC HEALTH ASSOCIATION

The annual meeting of the Massachusetts Public Health Association was held on January 28, with 85 members and guests present. The following officers were elected for 1937:

Ernest M. Morris, M.D., President
Curtis M. Hilliard, 1st Vice-President
Henry D. Chadwick, M.D., 2nd Vice-President
G. Donald Buckner, S.B., Secretary-Treasurer

Executive Committee

Harold D. Chope, M.D., Newton
William O. Hewitt, M.D., Attleboro
Wilbur N. O'Brien, Ph.C., Newburyport
L. Jackson Smith, M.D., Springfield
Charles F. Wilinsky, M.D., Boston

Dr. Henry D. Chadwick was re-elected representative to the Governing Council of the American Public Health Association.

Dr. Draper was unable to be present owing to the flood and conditions in the Middle West, and Dr. Gaylord W. Anderson, deputy commissioner, Massachusetts Department of Public Health, presented a summary of the legislation proposed by the Special Commission on Public Health Laws in Massachusetts.

At the annual meetings of the Sections the following section officers were elected:

Board of Health Section

William O. Hewitt, M.D., Attleboro, Chairman
Harold D. Chope, M.D., Newton, Secretary
John J. McGrath, Salem, Representative on Executive Committee

Laboratory Section

S. C. Dalrymple, M.D., Newton, Chairman
Roy F. Feemster, M.D., Boston, Vice-Chairman
John W. Williams, M.D., Cambridge, Secretary and Representative on Executive Committee

Child Hygiene and Public Health Nursing Section
Charlotte Raymond, Newton, Chairman
Margaret L. Boyle, R.N., Worcester, Secretary
Harold W. Stevens, M.D., Great Barrington, Representative on Executive Committee

Resolutions on the deaths of the three following members were adopted by a rising vote:

Harold Edson Miner, M.D., died September 15, 1936.

Edward H. Trowbridge, M.D., died January 21, 1937.

Charles Beaver Mack, M.D., died January 23, 1937.

MASSACHUSETTS HOSPITAL ASSOCIATION

The Massachusetts Hospital Association, which was temporarily organized a year ago, was made permanent recently, when a constitution and by-laws were approved, and the slate of officers elected at the first meeting was confirmed unanimously. The action took place, February 25, at the close of the first day of the New England Hospital Association's three-day annual meeting.

The re-elected officers are as follows: president, Dr. Henry M. Pollock of the Massachusetts Memorial Hospitals; vice-president, Bertha W. Allen, R.N., of the Newton Hospital; treasurer, Rev. Warren F. Cook of the New England Deaconess Hospital, and secretary, Dr. Norman C. Baker of the Massachusetts General Hospital.

NOTICES

REMOVAL

GEORGE K. FENN, M.D., announces the removal of his office to 19 Abbott Street, Beverly.

RHEUMATIC FEVER CLINIC AT THE ROBERT B. BRIGHAM HOSPITAL

There will be an open clinical meeting at the Robert B. Brigham Hospital, 125 Parker Hill Avenue, Boston, Tuesday evening, March 30, at 8 o'clock. Patients with rheumatic fever will be shown and a discussion on rheumatic fever will be given by Dr. T. Duckett Jones, physician-in-chief of the House of the Good Samaritan. Doctors and medical students are cordially invited to attend.

JOHN G. KUHNS, M.D., *Chief-of-Staff.*

TAG DAY FOR CANCER CONTROL

A tag day drive for cancer control will be held in Boston, March 27, as part of the state campaign for cancer control, which is being conducted under the auspices of the Women's Field Army of the American Society for the Control of Cancer. Boston headquarters of this organization have been opened at the Hotel Westminster, with Mrs. Carl F. Schrader, of Belmont, state commander, in charge.

Radio stations will cooperate in short announcements during the campaign, and there will be a nationwide broadcast on March 23, when leaders of thirty national organizations will speak. The work in Boston will be concentrated during Holy Week.

MEDICAL CLINIC AT THE PETER BENT BRIGHAM HOSPITAL

At 3:30 p. m. on Thursday, March 25, in the amphitheater of the Peter Bent Brigham Hospital, Dr. Harry Blotner, instructor in medicine, Harvard Medical School, and associate in medicine, Peter Bent Brigham Hospital, will give a medical clinic. Practitioners and medical students are cordially invited to attend.

CATHOLIC HOSPITAL ASSOCIATION

The officers and executive board of the Catholic Hospital Association of the United States and Canada have made the following announcements:

The twenty-second annual convention of the Association will be held at the Stevens Hotel, Chicago, June 14 to 18.

Two preconvention conferences will be held, the Conference on Hospital Administration on June 11 and 12, and the Conference on Nursing Education, June 12 and 13, at Loyola University, Chicago.

SERIES OF LECTURES ON ALCOHOLISM

The Social Service Committee of the Boston City Hospital and the Advisory Committee for the Study of Alcoholism (sponsors of the WPA Survey) have issued invitations to attend a series of lectures on various phases of the problem of alcoholism to be given in the amphitheater of the Mallory Institute of Pathology, 784 Massachusetts Avenue, Boston.

The first lecture was given on March 15. Other lectures, to be held on Monday evenings at 8 p. m., are as follows:

March 22—Hon. Joseph T. Zottoli, Associate Justice, Central Municipal Court. The Problem of Alcoholism in the Courts.

March 29—Dr. George R. Minot, Director, Thorndike Memorial Laboratory, Boston City Hospital. Dietary Deficiencies.

April 5 — Dr. H. Houston Merritt, Associate in Neurology, Harvard Medical School. Alcoholism and Diseases of the Nervous System.

April 12—Dr. Leo Alexander, Instructor in Neurology, Harvard Medical School. Neuropathological Aspects of Alcoholism.

April 26 — Dr. Timothy Leary, Medical Examiner, Southern Suffolk District. Alcoholism as a Medico-Legal Problem.

May 3—Miss Mildred G. Gray, Assistant in Pharmacology, Boston University School of Medicine. The Physiological Effects of Alcohol.

May 10—Dr. Jackson Thomas, Chief Medical Officer, Boston Psychopathic Hospital. Alcoholism and Mental Disease.

May 17 — Dr. Robert Fleming, Research Fellow, McLean Hospital, Waverley, Mass. The Treatment of Chronic Alcoholism.

May 24—Miss Mabel R. Wilson, Director of Medical Social Service, Boston City Hospital. Alcoholism as a Problem in Medical Social Service.

THE BOSTON DISPENSARY

25 Bennet Street

CLINICAL STAFF MEETING

A luncheon meeting of the clinical staff of the Boston Dispensary will be held on Tuesday, March 23, in the auditorium on the second floor of the Dispensary building, at 12 o'clock noon.

At 12:30 p. m. there will be a presentation and discussion of some orthopedic problems (with clinic cases to illustrate) by Dr. Louis A. O. Goddu, associate chief of the Orthopedic Department.

An invitation is extended to any who are interested in the subject. Luncheon to nonmembers, 35c.

OLIVER G. TINKHAM, M.D., *President*,
ALLEN R. BARROW, M.D., *Secretary*.

THE NEISSERIAN MEDICAL SOCIETY OF MASSACHUSETTS

The twelfth (sixth annual) meeting of the Neisserian Medical Society of Massachusetts will be held on Wednesday, March 31, at the Boston City Club, 14 Somerset Street.

Dinner 6:30 p. m. ($1.75 per plate.) Room U, tenth floor.

Meeting 8:00 p. m. Room U, tenth floor.

Election of officers.

PROGRAM

The Treatment of Gonorrhea in the Male. Part II. Details of Procedure. N. A. Nelson, M.D. (Paper based on answers to questionnaire.)

THE EXECUTIVE COMMITTEE.

THE NORFOLK DISTRICT MEDICAL SOCIETY

A regular meeting of the society will be held in the New England Deaconess Hospital Tuesday evening, March 30, at 8 p. m. Tel. ASP. 4620.

Business: 8:00 p. m.

Communications: 8:15 p. m.

A Survey of the Diabetic Work of the George F. Baker Clinic at the New England Deaconess Hospital. Elliott P. Joslin, M.D.; Howard F. Root, M.D.; Priscilla White, M.D.; Alexander Marble, M.D.; Allen P. Joslin, M.D.

This will be a symposium on diabetes with case presentations.

Discussion.

Collation.

FRANK S. CRUICKSHANK, M.D., *Secretary*.
1247 Beacon Street,
Brookline.

NEW ENGLAND PHYSICAL THERAPY SOCIETY

The regular meeting of the New England Physical Therapy Society will be held at the Hotel Victoria, 271 Dartmouth Street, Boston, on Wednesday evening, March 24, at 8 o'clock promptly.

Council Meeting at 6; Round Table Dinner at 6:30.

PROGRAM

Physical Therapy in Industrial Surgery. Dr. Joseph H. Shortell, Boston.

Discussion by Dr. Howard Moore, Dr. George E. Deering and Dr. William D. McFee.

All members of the medical profession are cordially invited to attend.

WILLIAM D. MCFEE, M.D., *Secretary*.
41 Bay State Road,
Boston.

MIDDLESEX SOUTH DISTRICT MEDICAL SOCIETY

A meeting of this district society will be held on Wednesday, March 31, at the Cambridge City Hospital.

The program, which will begin at 9 o'clock in the morning and will terminate at about 1 o'clock, when luncheon will be served, is as follows:

OPERATIONS—Dr. Harry H. Germain, Dr. Daniel F. Mahoney, Dr. Edward J. O'Brien, Dr. Edward T. Downey.

DRY CLINIC—Dr. Harry H. Germain—Results in three cases of gall bladder surgery.

Dr. Daniel F. Mahoney—Experiences with nephrectomy for pyonephrosis.

Dr. Edward J. O'Brien—Present status of transurethral resection of the prostate and actual demonstration of technic of operation.

Dr. Edward J. O'Brien — Mandelic acid in treatment of urinary infections.

Dr. Frederick W. O'Brien — X-ray treatment of carbuncles.

Dr. Bernard A. Godvin — Epiphyseal injuries of long bones and method of treatment.

Dr. Arthur F. Sargent — Treatment of low back strain.

Dr. William N. Lanigan—Fractures of the hip and methods of treatment.

Presentation of cases by Medical Department.

Dr. F. G. Miniter, Dr. T. E. Dinan, Dr. W. P. Hewitt—Presentation of three cases. *Streptococcus viridans* in blood stream following simple mastoidectomy. The use of prontosil in two cases of *Streptococcus hemolyticus* following simple mastoidectomy.

Dr. Maxwell E. Macdonald—When does a head injury call for surgical intervention? Spontaneous subarachnoid hemorrhage—its incidence and treatment.

Dr. William A. Noonan—Demonstration of inhalation anesthesia, carbon-dioxide filtrate method.

Dr. Joseph B. Rockett—Treatment of fractures of the jaw. Results in dental and nose and throat surgery with gas-oxygen anesthesia.

SUMNER H. REMICK, M.D., *President*,
ALEXANDER A. LEVI, M.D., *Secretary*.

THE AMERICAN NEISSERIAN MEDICAL SOCIETY

The third annual meeting of the American Neisserian Medical Society will be held on June 8, at the Senator Hotel, Atlantic City.

The program will consist of papers and discussions of the various phases of the management and control of gonorrhea. All who are interested are cordially invited to be present.

The meeting will begin promptly at 10:00 a. m. and will continue throughout the day.

OSCAR F. COX, JR., M.D., *Secretary.*

HARVARD MEDICAL SOCIETY

The next meeting of the Harvard Medical Society will be held in the Peter Bent Brigham Hospital amphitheater (Shattuck Street entrance), Tuesday evening, March 23, at 8:15 p. m.

PROGRAM

Presentation of Cases.

Hyperinsulinism. Allen O. Whipple, M.D., Valentine Mott Professor of Surgery, Columbia University College of Physicians and Surgeons, New York City.

Medical students and physicians are cordially invited to attend.

MARSHALL N. FULTON, M.D., *Secretary.*

SOCIETY MEETINGS, CONGRESSES AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING MONDAY, MARCH 22

Monday, March 22—

*8 p. m. Lecture on Alcoholism, Amphitheater of the Mallory Institute of Pathology, 784 Massachusetts Avenue, Boston.

Tuesday, March 23—

*9 a. m. - 10 a. m. Boston Dispensary, 25 Bennet Street, Boston. X-ray Demonstration. Dr. Alice Ettinger.

9:30 a. m. Massachusetts General Hospital. Thoracic Clinic, Ether Dome.

*12 m. Boston Dispensary, 25 Bennet Street, Boston. Clinical Staff meeting.

*8:15 p. m. Harvard Medical Society. Peter Bent Brigham Hospital Amphitheater (Shattuck Street Entrance).

Wednesday, March 24—

8 a. m. Massachusetts General Hospital. Grand Rounds, Orthopedic Department.

*9 a. m. - 10 a. m. Boston Dispensary, 25 Bennet Street, Boston. Hospital Case Presentation. Dr. S. J. Thannhauser.

†12 m. Clinicopathological Conference. Children's Hospital Amphitheater.

4 p. m. - 5 p. m. Surgical Pathological Conference. Dr. Cutler and Dr. Wolbach, Peter Bent Brigham Hospital.

*8 p. m. New England Physical Therapy Society. Hotel Victoria, 271 Dartmouth Street, Boston.

Thursday, March 25—

8 a. m. Massachusetts General Hospital. Circulatory Clinic Rounds.

*9 a. m. - 10 a. m. Boston Dispensary, 25 Bennet Street, Boston. Blood Clinic. Dr. Isadore Olef. Dr. Heinrich G. Brugsch.

11 a. m. Massachusetts General Hospital. Medical Grand Rounds, Ether Dome.

12 m. Massachusetts General Hospital. Clinicopathological Conference.

*3:30 p. m. Medical Clinic at the Peter Bent Brigham Hospital. Dr. Harry Blotner.

Friday, March 26—

*8:30 - 9:30 a. m. Exchange visit, Surgical and Orthopedic Staffs of the Peter Bent Brigham and the Children's Hospitals, held this week at the Children's Hospital. **Note change of day for this week only.**

*9 a. m. - 10 a. m. Boston Dispensary, 25 Bennet Street, Boston. Recent Advances in Cancer. Dr. Joseph Aub.

10 a. m. Massachusetts General Hospital. Fracture Rounds.

Saturday, March 27—

*9 a. m. - 10 a. m. Boston Dispensary, 25 Bennet Street, Boston. Hospital Case Presentation. Dr. S. J. Thannhauser.

*10 a. m. - 12 m. Staff Rounds at the Peter Bent Brigham Hospital. Conducted by Dr. Henry A. Christian.

*Open to the medical profession.
†Open to Fellows of the Massachusetts Medical Society.

March 19—Boston Pathological Society will meet at 8 p. m. in the Amphitheater (Vila Street entrance) of the Children's Hospital.

March 22 - May 24—Series of Lectures on Alcoholism. See page 488.

March 23—Harvard Medical Society. See page 490.

March 23—Boston Dispensary. Clinical Staff meeting. See page 489.

March 24—New England Physical Therapy Society. See page 489.

March 25—Medical Clinic at the Peter Bent Brigham Hospital. See page 488.

March 27—Tag Day for Cancer Control. See page 488.

March 29-31—First International Conference on Fever Therapy. See page 322, issue of February 18.

March 30—Rheumatic Fever Clinic at the Robert B. Brigham Hospital. See page 488.

March 31—Neisserian Medical Society of Massachusetts. See page 489.

April 8—Pentucket Association of Physicians. Hotel Bartlett, 95 Main Street, Haverhill, at 8:30 p. m.

April 12-16—The Postgraduate Institute of the Philadelphia County Medical Society. See page 185, issue of January 28.

April 16—William Harvey Society, 8 p. m. in the Auditorium of the Beth Israel Hospital, Boston.

April 21-24—American Society for Experimental Pathology. See page 1075, issue of May 21.

June 8 and 9—American Board of Obstetrics and Gynecology. See page 78, issue of January 14.

June 8—The American Neisserian Medical Society. See page 489.

June 11-18—Catholic Hospital Association. See page 488.

July 6-11—Fifth International Congress of Hospitals. See page 37, issue of January 7.

October 5-8—American Public Health Association Meeting. New York City.

October 25-29—American College of Surgeons. Chicago, Illinois.

DISTRICT MEDICAL SOCIETIES

ESSEX SOUTH DISTRICT MEDICAL SOCIETY

April 7—Essex Sanatorium, Middleton. Clinic at 5 p. m. Dinner at 7 p. m. Speaker: Dr. Francis B. Trudeau of Saranac Lake, New York. Subject: Personal Reminiscences of a Son of a Distinguished Father. (Illustrated.)

May 12—Annual Meeting. Salem Country Club. Speaker: Dr. P. P. Johnson of Beverly. Subject: A Trip to the Bahamas and Guatemala. (Illustrated.)

R. E. STONE, M.D., Secretary.
74 Lothrop Street, Beverly.

FRANKLIN DISTRICT MEDICAL SOCIETY

Will meet at the Weldon in Greenfield at 11 a. m. the second Tuesday of May.

CHARLES MOLINE, M.D., Secretary.
Sunderland.

MIDDLESEX EAST DISTRICT MEDICAL SOCIETY

May 11—Bear Hill Golf Club, Stoneham.

KENNETH L. MACLACHLAN, M.D., Secretary.
1 Bellevue Avenue, Melrose.

MIDDLESEX SOUTH DISTRICT MEDICAL SOCIETY

March 31—See page 489.

NORFOLK DISTRICT MEDICAL SOCIETY

March 30—See page 489.

May—Annual Meeting. Details to be announced.

Note: The Censors will meet for the examination of candidates on the first Thursday of May. Fee of $10.00 is payable at the time of examination. Application blanks may be obtained by writing the Secretary, furnishing name, address and name of school of graduation in medicine. Application must be made at least three weeks prior to date of examination. Candidates whose applications are on file will receive proper notices.

FRANK S. CRUICKSHANK, M.D., Secretary.
1247 Beacon Street, Brookline.

PLYMOUTH DISTRICT MEDICAL SOCIETY

March 18—11 a. m. Brockton Hospital.
April 15—Annual Meeting. 11 a. m. Ducy Hospital.
May 20—11 a. m. Lakeville State Sanatorium.

FRED F. WEINER, M.D., Secretary.
231 Main Street, Brockton.

SUFFOLK DISTRICT MEDICAL SOCIETY

March 31—Boston Medical Library, 8 Fenway, at 8:15 p. m.

April 28—Annual Meeting. Boston Medical Library. 8:15 p. m. "Problems in Surgical Diagnosis." Dr. Howard M. Clute.

CONRAD WESSELHOEFT, M.D., President,
CHARLES C. LUND, M.D., Secretary.

WORCESTER DISTRICT MEDICAL SOCIETY

April 14—Worcester Hahnemann Hospital, Worcester. 6:15 p. m.: Dinner—complimentary by the hospital. 7:30 p. m.: Business session and scientific program.

May 6—At 4:30 in the rooms of the Worcester Medical Library, Inc., at 34 Elm Street, Worcester, will be held the spring meeting of the Board of Censors.

Wednesday Afternoon and Evening, May 12—Annual Meeting. Time and place for this meeting will be announced in an early spring issue of the Journal.

ERWIN C. MILLER, M.D., Secretary.
27 Elm Street, Worcester.

BOOK REVIEWS

Live Long and Be Happy. How to Prolong Your Life and Enjoy It. Lewellys F. Barker. 224 pp. New York and London: D. Appleton-Century Company. $2.00.

Dr. Barker has written this book for laymen. Free from confusing scientific terms it brings dependable medical information with the later developments, in popular and readable language. The causes of disease are discussed, particularly those that are important in prevention of disease and the prolongation of life. The reader will find here an authoritative work, devoid of sensationalism and pseudodrama, characterizing much of present-day health advice.

Contraception as a Therapeutic Measure. Bessie L. Moses. 106 pp. Baltimore: The Williams & Wilkins Company. $1.00.

Even though most clinics agree that the occlusive vaginal diaphragm, with or without jelly, is the best method of birth control for the vast majority of patients, it has always been a difficult matter to get a completely unprejudiced set of figures as to its efficacy.

Realizing this lack of trustworthy statistics, the Bureau for Contraceptive Advice was formed in Baltimore at the suggestion of a small group of men connected with Johns Hopkins University to collect the necessary data on about 1,000 cases, and this book is a comprehensive and detailed exposition of its work.

For anyone interested in the subject it will prove an invaluable source of material. Besides the presentation of the actual results there is an extensive bibliography and also an appendix showing the various printed forms used by the Bureau.

It is perhaps of interest briefly to compare some of the Baltimore figures with analogous ones collected by the Mothers' Health Office, sponsored by the Birth Control League of Massachusetts. The figures for the latter clinic are taken from their annual report April 1, 1935, to April 1, 1936, and the comparison made in the following table.

	Baltimore		Boston	
	Number	%	Number	%
Total cases	1069		*1229	
Pregnancies in cases using method	65	6.1	78	6.3
Patients admitting carelessness	36	3.4	55	4.4
Failure of method	29	2.7	23	1.9

*New patients admitted since clinic opened.

It will be seen that both clinics have a comparable number of cases, each over 1,000. Of these a certain number became pregnant while using the contraceptive device recommended. The percentages for Baltimore and Boston are almost identical, 6.1 and 6.3, respectively. Other pregnancies did occur in patients coming to the clinics and in Baltimore the not insignificant number of 169 of these additional pregnancies occurred in patients who abandoned the method as being too cumbersome or for some other reason. Of the patients who claimed to have used the method and who nevertheless became pregnant, 36 in Baltimore and 55 in Boston admitted carelessness, and 29 and 23, respectively, maintained that they had become pregnant while using the method carefully and faithfully. This discrepancy in the two cities can only be explained on the assumption that Boston patients are more honest than their Baltimore sisters.

On the basis of these figures the following conclusions seem justifiable.

1. With careful instruction and follow-up in proper cases where the work is done by a trained personnel, one can count on no more than 93-94 per cent success in contraception.

2. Those who report greater success than this are either deluding themselves or their figures are voided by lack of adequate follow-up.

Vascular Disorders of the Limbs. Described for Practitioners and Students. Sir Thomas Lewis. 111 pp. New York: The Macmillan Company. $2.00

This relatively small volume of one hundred pages is a refreshingly clear presentation of the abnormal arterial conditions encountered in the extremities. It does not attempt to describe circulatory difficulties of the venous system or those referable to aneurysm because of "the excellent accounts of such maladies that are already available". The author has devoted a considerable portion of the book to a review of the physiology of the peripheral circulation under both normal and abnormal conditions. So successfully has this phase of the problem been dealt with, both in its general and specific consider-

ations, that the reader is equipped with a sound fundamental understanding on which to institute corrective measures.

The treatment follows the description of each condition, and the author has studiously attempted to evaluate the efficacy of the various known forms of therapy. He has wisely minimized the value and importance of complicated and expensive pieces of apparatus as aids in diagnosis and treatment and has laid stress on simple procedures that would be available to students and practitioners for whom the book was arranged.

To those especially interested in the subject, certain features are of interest by virtue of the very discussion they provoke. Thus the failure to mention Buerger exercises would seem to some an important omission, and the just criticism of the operation of cervical sympathectomy without reference to the more recent type of dorsal operation for this same group of cases would likewise seem unfortunate.

The orderly sequence of the book is of aid in following the presentation of the subject and the inclusion of a complete index helps to a great extent the ready reference to any special point of interest.

Collected Writings. Alfred F. Hess. Volumes I and II. 719 pp. and 734 pp. Springfield and Baltimore: Charles C Thomas. $15.00.

The papers and addresses in memory of Dr. Alfred Fabian Hess, published in two volumes, stand out prominently as an example that a "physician may carry along the practice of pediatrics and at the same time be a genuine contributor to the progress of Science". In these volumes there are two hundred and twenty-seven articles which Alfred Hess wrote between 1905 and 1933. As these writings are arranged chronologically, they serve excellently to acquaint the reader with the amazing number of fields which have been cultivated during the past twenty-five years by his creative and tireless search after new knowledge pertaining to the health and welfare of children. Of particular significance is the Biographical Memoir written by Dr. Abraham Flexner, wherein are set forth *the methods of work* which without question enabled Dr. Hess to become recognized as one of the great investigators in clinical medicine.

It would be impossible, in the space allotted to this review, to mention the vast number of topics which are here collected, from his earliest writing, "Fatal Obliterating Endophlebitis of the Hepatic Veins" and his papers on infantile tuberculosis which resulted in the founding of the first sanatorium for infants with tuberculosis, to his epoch-making discoveries concerning the nature of vitamins and the deficiency diseases, which occupied much of his working time in the latter years. Upon these subjects he speaks with authority and his published monographs on rickets, osteomalacia, scurvy and tetany will be held as classic for all time. Herein are to be found subjects relating to the diagnosis and treatment of disease, and, as well, original discoveries obtained from the application of the fundamental sciences—bacteriology, chemistry, histopathology and physiology—to the nature and cure of childhood diseases. Although "Hess himself was not really a master of any one special method of investigation, physicians and students would find their time well rewarded by reading these contributions."

The Clinical Use of Digitalis. Drew Luten. 226 pp. Springfield and Baltimore: Charles C Thomas. $3.50.

For the past dozen years Dr. Luten has been publishing the results of his studies on the influence of digitalis on the human subject. This book, however, is not simply the summary of his own experience but a concise survey of modern work on digitalis therapy. It answers many clinical questions and where the answers have not yet been found the evidence is clearly presented for the reader's own interpretation. The chapters concern such ever-vital subjects as the effect of digitalis on the ventricular muscle, the A-V tissues, the pacemaker, and the blood vessels. Its diuretic, electrocardiographic, and toxic actions are discussed, as well as the indications for its use, dosage, dangers and relations to prognosis. Much stress is put upon the fact that digitalis must not be considered of value only in the presence of auricular fibrillation but that its beneficial effect is upon the heart muscle, and it is, therefore, of great value in the presence of normal rhythm. Indeed the author's present view is that its main benefit in the presence of auricular fibrillation is not through the blocking of impulses in the A-V tissues but in improving the tonus of the ventricles and in decreasing their irritability, the slowing of the ventricular rate being a result and not the main cause of the improvement in cardiac action. Where auricular fibrillation is not associated with heart failure, digitalis therapy, in many cases, has little effect in slowing the ventricular rate. He deprecates overemphasis upon the electrocardiograph in determining digitalis dosage—a well-taken point. Consistent with the best present clinical usage he believes congestive failure to be the indication for digitalis irrespective of the cardiac rhythm. Individualism in dosage, taking into account all the variables, is the price of success in therapy and the avoidance of toxic reactions. The average full dose for digitalization of an adult of 150 pounds is about 30 grains, corresponding closely with Withering's original estimate. The statement that the degree of favorable reaction to digitalization is a notable guide to prognosis would certainly be generally conceded. The final chapter consists of brief "Therapeutic Theses" which summarize the book, and the bibliography of 132 modern references is well selected. The book fills a real need for practitioners concerned with the clinical action of digitalis, and, among internists, who, indeed, is not?